No.

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

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

In *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398 (2007), this Court rejected the use of "mandatory formulas" to determine whether a patent would have been obvious under 35 U.S.C. § 103 and instructed that courts must take an "expansive and flexible approach" to the obviousness inquiry in *all* patent cases. Despite those clear directives, the Federal Circuit has continued to apply an inflexible and formalistic "lead compound" test as the exclusive standard for determining obviousness of chemical compositions. The question presented is:

> Whether the Federal Circuit's rigid application of the "lead compound" test to determine whether a patent directed to a chemical composition would have been obvious under 35 U.S.C. § 103 conflicts with *KSR* and impermissibly creates different patentability standards for chemical and non-chemical inventions.

RULE 29.6 STATEMENT

The ultimate parent of petitioners Apotex Inc. and Apotex Corp. is Sherfam Inc., which is not publicly traded. No publicly traded company owns 10% or more of the shares of petitioners or of any of their parent corporations.

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PETITION FOR A WRIT OF CERTIORARI

OPINIONS BELOW

The opinion of the court of appeals (App., *infra*, 1a-24a) is reported at 655 F.3d 1352. The summary-judgment opinion of the United States District Court for the Southern District of New York (App., *infra*, 43a-79a) is unreported. The opinion of the district court reinstating its summary-judgment order (App., *infra*, 25a-42a) is also unreported.

JURISDICTION

The court of appeals issued its decision on August 25, 2011. On November 7, 2011, Chief Justice Roberts extended the time within which to file a petition for a writ of certiorari until December 23, 2011 (No. 11A461). On December 6, the Chief Justice granted a further extension of time to and including January 13, 2012. This Court's jurisdiction is invoked under 28 U.S.C. § 1254(1).

STATUTORY PROVISION INVOLVED

35 U.S.C. § 103(a) provides in pertinent part:

> A patent may not be obtained . . . if 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. Patentability shall not be negatived by the manner in which the invention was made.

STATEMENT

This case presents a valuable opportunity for this Court to address a significant and recurring error made by the Federal Circuit in cases involving the validity of patents on chemical compounds—patents with extraordinary implications for the national economy and patient health. The underlying litigation involves a challenge to the validity of a patent on a pharmaceutical nasal spray. In the decision below, the Federal Circuit held that the disputed patent was not invalid for obviousness even though the patented composition is an intentional copy of another commercially successful nasal spray containing the same active ingredient in exactly the same concentration.

In reaching that conclusion, the Federal Circuit applied the "lead compound" test. That test—a virtually insurmountable standard that the Federal Circuit applies *only* to patents on chemical compositions—requires a patent challenger to demonstrate both the existence of a motivation to select a particular lead compound from the prior art *and* a motivation to make specific modifications to that lead compound to arrive at the composition covered by the challenged patent. The Federal Circuit has defended its rigid test on the ground that the chemical arts are somehow inherently less predictable than every other field of endeavor and therefore require a qualitatively different patentability threshold.

In *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398, 419 (2007), this Court squarely rejected the use of "mandatory formulas" to determine whether a patent is invalid for obviousness under 35 U.S.C.

§ 103(a). This Court also instructed that a patent can be invalid for obviousness because it would have been "obvious to try" combining known ingredients. 550 U.S. at 421. The "lead compound" test employed by the Federal Circuit conflicts with both of those directives. As a result, the Federal Circuit routinely extends protection to patents—like the one at issue here—covering inventions "that would occur in the ordinary course without real innovation." *Id.* at 419. This Court should take this opportunity to correct the Federal Circuit's erroneous application of the Court's precedents and the Nation's patent laws.

A. The Patent-in-Suit

The patent at issue in this case—U.S. Reissue Patent No. RE40,812 ("the '812 patent")—is directed to a liquid pharmaceutical product containing the active ingredient salmon calcitonin. App., *infra*, 3a, 44a. Respondent Unigene Laboratories, Inc., owns the '812 patent[1] and manufactures its commercial embodiment, which is sold in the United States by respondent Upsher-Smith Laboratories under the trademark Fortical®. *Id.* at 3a, 45a.

Fortical® is a calcitonin nasal spray prescribed to treat postmenopausal osteoporosis, a bone disease

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[1] Unigene owns the '812 patent through assignment from its named inventor, Dr. William Stern. App., *infra*, 3a. The '812 patent is a reissue of U.S. Patent No. 6,440,392 ("the '392 patent"), entitled "Nasal Calcitonin Formulations." *Ibid.* Before the commencement of litigation in this case, Unigene filed a reissue application with the U.S. Patent and Trademark Office ("USPTO") to correct a defect in the '392 patent. The USPTO granted that application during the pendency of the district court proceedings in this case. *Id.* at 3a, 46a. The reissue proceedings are not at issue here.

associated with improper calcium levels. Calcitonins are naturally occurring hormones that help regulate calcium ions in the blood. Because of their role in regulating calcium, calcitonins are known to be useful for treating calcium-related conditions such as osteoporosis. App., *infra*, 4a. Indeed, since 1995—long before the '812 patent application was filed—a calcitonin nasal spray called Miacalcin® has been successfully marketed by another pharmaceutical company for the treatment of postmenopausal osteoporosis. *Id.* at 3a.

Fortical® was designed to imitate Miacalcin®. App., *infra*, 60a-61a n.11. It contains the same active ingredient as Miacalcin®—salmon calcitonin—in the exactly the same concentration (2,200 I.U./mL). *Id.* at 3a-4a. Indeed, Fortical® is a "bioequivalent" of Miacalcin®, which means that the two drugs affect the body and perform in precisely the same manner. *Id.* at 3a. The only difference between the two formulations is found in their *inactive* ingredients, which do not alter the way that the two compositions perform to treat osteoporosis.

Unigene sought to develop a bioequivalent copy of Miacalcin® to take advantage of the favorable regulatory treatment that generic drugs enjoy under the federal food and drug laws. App., *infra*, 19a, 60a-61a n.11. The Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the "Hatch-Waxman Act," governs the FDA approval process of brand-name and generic drugs. Pub. L. 98-417, 98 Stat. 1585 (1984). A primary objective of the Act is "to make available more low cost generic drugs" by streamlining the approval process for generic drugs and rewarding

generic drug companies that challenge brand-name manufacturers' use of dubious patent claims to ward off generic competition. H.R. Rep. No. 98-857, pt. 1 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2647.

To obtain approval of an innovative drug product, brand-name manufacturers must submit to the U.S. Food and Drug Administration ("FDA") a New Drug Application ("NDA") containing detailed pharmacological and clinical information demonstrating that the drug proved safe and effective in a rigorous testing regime. See 21 U.S.C. § 355(b)(1). The Hatch-Waxman Act created two approval pathways through which manufacturers of copies of previously approved drugs can avoid the onerous NDA process. Under the first pathway, manufacturers of identical versions of previously approved drugs can file an Abbreviated New Drug Application ("ANDA") showing that the proposed drug product is bioequivalent to an approved brand-name drug. The ANDA relies on the same clinical safety and efficacy data used to support the brand-name drug's NDA, thus eliminating the costly and time-consuming duplication of clinical studies. See *id.* § 355(j).

Under the second regulatory pathway, manufacturers of close (but not identical) copies of previously approved drug products can file a so-called "paper NDA" under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. See 21 U.S.C. § 355(b)(2). Although a paper NDA must include some safety and efficacy information, it can rely in part on the FDA's findings of safety and efficacy for a previously approved drug—again streamlining the

approval process.[2] One of the advantages of filing a paper NDA is that the manufacturer can "design around" the patent covering the brand-name drug by making small modifications to the drug formulation such that the follow-on drug will not infringe the patent on the innovator drug.

The named inventor of Fortical®, Dr. William Stern, sought to create a bioequivalent of Miacalcin® so that respondents could quickly gain FDA approval of their version of Miacalcin® through one of the streamlined approval pathways for generic drugs. To that end, Dr. Stern started with the same active ingredient contained in Miacalcin®—salmon calcitonin—and modified only its inactive ingredients. App., *infra*, 4a, 19a, 61a n.11.

Miacalcin® contains the inactive ingredient benzalkonium chloride ("BZK"), which functions as a preservative, as a surfactant (a compound that lowers the surface tension of a liquid), and as an absorption enhancer. App., *infra*, 4a.[3] To develop Fortical®, Dr. Stern simply replaced the BZK used in Miacalcin® with other inactive ingredients known to perform the same functions. Thus, as a substitute for BZK in Miacalcin®, Fortical® contains benzyl alcohol and phenylethyl alcohol, which act as preservatives; polysorbate 80, which acts as a

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[2] Filers of an ANDA or paper NDA can also, in certain circumstances, receive the benefit of market exclusivity—a period of time in which the follow-on drug is the only copy of an innovator drug allowed on the market. See 21 U.S.C. § 355(j)(5)(B)(iv); *id.* § 355(j)(5)(F)(iii), (iv).

[3] Miacalcin® also contains sodium chloride, nitrogen, and hydrochloric acid. App, *infra*, 4a. Those inactive ingredients are not relevant to the issues raised in this case.

surfactant; and, of particular relevance here, citric acid, which acts as an absorption enhancer and a buffer. *Id.*

In both Miacalcin® and Fortical® the absorption enhancer serves to increase the bioavailability of calcitonin—*i.e.*, the amount of calcitonin that crosses the nasal membrane and enters the patient's blood stream. A prior patent (U.S. Patent No. 5,912,014) covering a compound invented by Dr. Stern (which was assigned to respondent Unigene) showed that citric acid enhances bioavailability of salmon calcitonin. In developing Fortical®, Dr. Stern therefore replaced BZK—the absorption enhancer in Miacalcin®—with citric acid at a concentration that ensured that Fortical® delivers to patients the same amount of calcitonin as does Miacalcin®. App., *infra*, 6a, 19a.

The Fortical® composition that resulted from Dr. Stern's modification of Miacalcin® is covered by claim 19 of the '812 patent, the only patent claim at issue in this case. That claim recites:

> A liquid pharmaceutical composition for nasal administration comprising about 2,200 MRC units of salmon calcitonin, about 20 mM citric acid, about 0.2% phenylethyl alcohol, about 0.5% benzyl alcohol, and about 0.1% polyoxyethylene(2) sorbitan monooleate.

App., *infra*, 5a (citing '812 patent col. 18 ll. 1-5).

Unigene sought FDA approval for its Fortical® product by filing a paper NDA under Section 505(b)(2). That application cited Miacalcin® as the "reference listed drug"—*i.e.*, the innovator drug that Fortical® was designed to imitate. See U.S.

Food and Drug Administration, NDA No. 21-406 (approved Aug. 12, 2005), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021406s000TOC.cfm.

B. The District Court Proceedings

Petitioners Apotex Inc. and Apotex Corp. (collectively "Apotex") manufacture and distribute generic drugs. In June 2006, Apotex filed with the FDA an ANDA seeking approval to manufacture and sell a generic version of Fortical®. As authorized by the Hatch-Waxman Act, Apotex submitted with its ANDA a certification stating that the '812 patent is invalid. App., *infra*, 4a-5a; see 21 U.S.C. § 355(j)(2)(A)(vii)(IV). The filing of such a certification constitutes an act of patent infringement. 35 U.S.C. § 271(e)(2)(A).

Respondents Unigene Laboratories and Upsher-Smith Laboratories (collectively "Unigene") sued Apotex for infringement in the U.S. District Court for the Southern District of New York. Apotex moved for summary judgment on the ground that claim 19 was invalid for obviousness. App., *infra*, 2a, 78a; see 35 U.S.C. § 282(2).

A patent is invalid as obvious "if 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." 35 U.S.C. § 103(a). "The ultimate judgment of obviousness is a legal determination." *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398, 427 (2007).

Before 2007, the Federal Circuit determined the ultimate question of obviousness by employing an approach referred to as the "teaching, suggestion, or motivation" test ("the TSM test"). That test required challengers to prove obviousness by identifying some specific teaching, suggestion, or motivation to combine previously known elements to arrive at the patented invention. In *KSR*, this Court rejected the Federal Circuit's "rigid" application of the TSM test, emphasizing that the use of "mandatory formulas" to determine obviousness conflicts with this Court's precedents and improperly "limits the obviousness inquiry." *Id.* at 419.

In sharp contrast to the "mandatory formula[]" employed by the Federal Circuit, this Court in *KSR* explained that it has always taken an "expansive and flexible approach" to the obviousness question. 550 U.S. at 415. That holistic approach requires a "broad inquiry" into the "interrelated teachings of multiple patents" and must "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 415, 418; see also *id.* at 420 ("Common sense teaches . . . that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle.").

KSR also clarified that one way that a patent can be proved obvious is by showing that a claimed combination of previously known elements would have been "obvious to try." The Court explained:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of

> ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance, the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR, 550 U.S. at 421.

In this case, Apotex argued that a hypothetical person having ordinary skill in the art ("PHOSITA") would have been motivated to copy the commercially successful Miacalcin® nasal spray by developing an analogous nasal spray that used the same active ingredient in the same concentration. Apotex argued that claim 19 is invalid because it would have been obvious to a PHOSITA to remove the inactive ingredients in Miacalcin® and replace them with other inactive ingredients that were already known to perform the same functions. App., *infra*, 60a-62a. Specifically, a PHOSITA would have known that the surfactant function of BZK could be replaced by polysorbate 80; that the preservative function of BZK could be replaced by benzyl alcohol and phenylethyl alcohol; and that the absorption-enhancement function of BZK could be replaced by citric acid.

The district court rejected Apotex's argument that claim 19 would have been obvious. App., *infra*, 43a-79a. The court explained that, under the "lead compound" test fashioned by the Federal Circuit, a challenger to a chemical patent must demonstrate that a PHOSITA would have been motivated not only to select a lead compound from the prior art but also to make specific modifications to that lead compound to arrive at the patent-in-suit. *Id.* at 55a-56a. Citing

several pre-*KSR* Federal Circuit opinions, the district court further stated that, "to establish obviousness, 'a claimed specific compound' must be '*precisely* envisioned' by the prior art.'" *Id.* at 54a (quoting *In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995) (emphasis added)); see App., *infra*, 54a ("'[W]hen a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references.'") (quoting *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998)).

Applying this "lead compound" test, the district court concluded that "little to none" of the prior art *specifically suggested* using citric acid as a replacement for BZK, the absorption enhancer in Miacalcin®. App, *infra*, 76a. The court further concluded that the *precise* "road from Miacalcin to Claim 19 was not *suggested* by the prior art." *Ibid.* (emphasis added). On that basis, the court held that claim 19 was not invalid for obviousness. *Id.* at 77a.

C. The Court of Appeals' Decision

The Federal Circuit affirmed. App., *infra*, 1a-24a. The court began its obviousness analysis by re-affirming the "lead compound" test for determining the obviousness of chemical compositions. App., *infra*, 18a. Indeed, the court held that the "lead compound" test applies even where (as here) the patented composition is a deliberate imitation of a previously approved drug:

> In the context of a composition or formulation patent where the patented formulation was made to mimic a previously FDA-approved formulation, the functional and pharmaceutical properties of

> the "lead compound" can be more relevant than the actual chemical structure (though not always mutually exclusive). Thus, the term "reference composition" is more appropriate than "lead compound" when considering obviousness for a chemical composition that the infringer deliberately imitates. In this case, Miacalcin® serves as the "reference composition" for Dr. Stern's development of the claimed composition.

Ibid. The Federal Circuit therefore extended the reach of its "lead compound" test to patents on chemical *formulations* (as opposed to chemical compounds)—even formulations in which the chemical compound itself is identical to a prior-art chemical compound.

The Federal Circuit acknowledged that "[c]laim 19 of the '812E patent is the result of Dr. Stern's effort to design around Miacalcin®" and that a person of ordinary skill in the art would have been motivated to create a bioequivalent of Miacalcin® to secure easy approval from the FDA to market an alternative to Miacalcin®. App., *infra*, 18a-19a. Applying the heightened standard required to show obviousness under the rigid "lead compound" test, however, the court of appeals concluded that a PHOSITA would *not* have been motivated to modify the "reference composition" Miacalcin® *in the precise way* that it was modified in claim 19.

Specifically, the court determined that a hypothetical PHOSITA would not have been motivated to replace the BZK used as an absorption enhancer in Miacalcin® with the 20mM of citric acid recited in claim 19. App., *infra*, 20a-23a. The court reached that conclusion even though Apotex cited

several prior-art patents—including one covering an invention by Dr. Stern, the inventor of claim 19—disclosing the use of citric acid to increase absorption of salmon calcitonin. The court concluded that no *single* patent cited by Apotex would have motivated a PHOSITA to use the specific concentration of citric acid described in claim 19 as a replacement for the BZK used in Miacalcin®. The court did not consider whether it would have been "obvious to try" using 20mM citric acid as an absorption enhancer based on the interrelated teachings of multiple prior-art patents. The court did not address the statement in *KSR* that "in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." 550 U.S. at 420.

REASONS FOR GRANTING THE PETITION

Under the Patent Act, "[a] patent may not be obtained" if its "subject matter as a whole" is "obvious" when judged in light of the prior art. 35 U.S.C. § 103(a). Enforcing this limit on patents is essential to "promot[ing] the Progress of Science and useful Arts." U.S. CONST. Art. I, § 8, Cl. 8. As this Court has repeatedly recognized, "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility." *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398, 419 (2007). Conferring monopoly rights on minor advances that are unworthy of such protection would also contradict the intentions of the Framers, whose "abhorrence of monopoly" drove them to ensure that patent protection would not be granted for "small details

[or] obvious improvements." *Graham* v. *John Deere Co.*, 383 U.S. 1, 7-9 (1966) (discussing writings of Thomas Jefferson, the "first administrator of our patent system" and "the author of the 1793 Patent Act").

Over the years, this Court has repeatedly "instruct[ed]" the lower courts concerning "the need for caution in granting a patent based on the combination of elements found in the prior art." *KSR*, 550 U.S. at 415. "For over a half century," the Court noted in *KSR*, it "has held that a 'patent for a combination which only unites old elements with no change in their respective functions . . . obviously withdraws what already is known into the field of its monopoly and diminishes the resources available to skillful men.'" *Id.* at 415-16 (quoting *Great Atlantic & Pacific Tea Co.* v. *Supermarket Equipment Corp.*, 340 U.S. 147, 152-53 (1950)). In the decision below, the Federal Circuit upheld the validity of a patent on a nasal spray that was an intentional copy of another commercially successful spray containing exactly the same active ingredient in exactly the same concentration. It did so based on a rigid and formalistic "lead compound" test that the Federal Circuit employs as the exclusive standard for determining obviousness of chemical compositions.

Review is warranted because the inflexible "lead compound" test conflicts in multiple respects with the teachings of *KSR* and extends patent protection to "inventions" that—like the one at issue here—"would occur in the ordinary course without real innovation." *KSR*, 550 U.S. at 419. The issue has significant consequences for the economy and public

health, is recurring, and amply deserves this Court's review.

I. The Federal Circuit's Rigid And Formalistic "Lead Compound" Test Conflicts With *KSR* And Sets An Inappropriately High Standard For Proving Obviousness In Chemical-Composition Cases

In *KSR*, the Federal Circuit had deployed a series of doctrines to avoid concluding that a patent was invalid for obviousness, even though the invention—titled "Adjustable Pedal Assembly With Electronic Throttle Control"—was simply a mechanical combination of two already well-known components. See 550 U.S. at 406, 413-15. The Federal Circuit considered it irrelevant "[t]hat it might have been obvious to try the combination of [an adjustable pedal assembly] and [an electronic] sensor," reasoning that "'obvious to try' has long been held *not* to constitute obviousness." *Id.* at 414 (internal quotation marks omitted; emphasis added). This Court emphatically disagreed, explaining that in certain circumstances "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* at 421.

As noted above, this Court in *KSR* also rejected the Federal Circuit's "rigid" application of the TSM test, under which those challenging a patent's validity on obviousness grounds were required to identify some specific "teaching, suggestion, or motivation" to combine previously known elements to arrive at the patented invention. This Court criticized the Federal Circuit's use of "mandatory formulas" to determine obviousness, explaining that

such formulaic and inflexible "tests" not only conflict with this Court's precedents but also improperly "limit[] the obviousness inquiry." 550 U.S. at 419. Instead of employing a "mandatory formula[]," the Federal Circuit should have taken an "expansive and flexible approach" to the obviousness question. *Id.* at 415. The proper approach requires a "broad inquiry" into the "interrelated teachings of multiple patents" and must "take account of the inferences and creative steps that a person of ordinary skill would employ." *Id.* at 415, 418.

A. The "Lead Compound" Test Is A "Mandatory Formula" That Applies Categorically And Exclusively To Chemical Compositions Of Matter

The "lead compound" test—which the Federal Circuit categorically applies to chemical composition cases—has two parts. First, the challenger must show that a hypothetical person having ordinary skill in the art ("PHOSITA") would have been motivated to select a lead compound as a starting point. Second, after surmounting that threshold, the challenger must show that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Takeda Chem. Indus., Ltd.* v. *Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57, 1363 (Fed. Cir. 2007) (internal quotation marks omitted); see also *Eisai Co.* v. *Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356 (Fed. Cir. 2008); *Procter & Gamble Co.* v. *Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009).

The Federal Circuit applied the "lead compound" test in this case. App., *infra*, 18a-23a. Indeed, the court explained that this test—which requires a threshold showing that a PHOSITA would have been motivated to select a lead compound as a starting point—applies even where (as here) the patented compound is, for regulatory reasons, a *deliberate imitation* of a previously approved drug. The Federal Circuit recognized that "the Hatch-Waxman Act encourages and rewards replication of protected compounds in some circumstances." App., *infra*, 20a. The court further acknowledged that such replication "rarely . . . lead[s] to innovative products." *Ibid.* Nevertheless, the court went on to conclude that under step two of the "lead compound" test a PHOSITA would *not* have been motivated to modify the "reference composition" Miacalcin® *in the precise way* that it was modified in claim 19. In particular, the Federal Circuit held that a hypothetical PHOSITA would not have been motivated specifically to replace the BZK used as an absorption enhancer in Miacalcin® with the 20mM of citric acid recited in claim 19. App., *infra*, 20a-23a.

The Federal Circuit applies the "lead compound" test exclusively to chemical composition cases because the court assumes that the chemical arts—unlike every other field of endeavor—are inherently "unpredictable." *Eisai*, 533 F.3d at 1359; *Procter & Gamble*, 566 F.3d at 996. As a result of that flawed assumption, the Federal Circuit does not apply the "lead compound" test (or any equivalent test) to any other category of patentable subject matter (including processes, machines, or manufactured goods). See 35 U.S.C. § 101. Thus, in mechanical cases, the court does not ask whether a person of

skill in the art would have been motivated first to choose a "lead machine" and then to make the specific modifications necessary to achieve the claimed machine. See, *e.g.*, *Wyers* v. *Master Lock Co.*, 616 F.3d 1231, 1237-45 (Fed. Cir. 2010) (in case involving obviousness of mechanical car hitches, making no mention of "lead machine"). Nor does the court apply the "lead compound" rule (or any equivalent test) to compositions of matter outside of the chemical arts. See, *e.g.*, *Muniauction, Inc.* v. *Thomson Corp.*, 532 F.3d 1318, 1324-28 (Fed. Cir. 2008) (in case involving software patent, making no mention of "lead software"). Rather, the Federal Circuit applies that approach to one category of patentable subject matter (compositions of matter) and, even then, to only one type of patentable subject matter (chemical compositions).

The clear lesson of *KSR*, however, is that courts must approach the obviousness inquiry on a case-by-case basis. It is difficult to imagine anything *more* "rigid"—and thus contrary to the "expansive and flexible" approach demanded by *KSR*—than the categorical application of a specific obviousness test only to patents within a specific field without regard to the nature of the problem to be solved, the content and scope of the prior art, or any other factor specific to the actual patent in question. "Application of categorical rules without focus on specific facts risks a return to pre-*KSR* precedent and analysis in broad subject matter areas—an exception that threatens to swallow the rule of *KSR*." Marian Underweiser, *Presumed Obvious: How* KSR *Redefines The Obviousness Inquiry To Help Improve The Public Record Of A Patent*, 50 INTELL. PROP. L. REV. 247, 303 (2010); see also *In re Durden*, 763 F.2d 1406,

1411 (Fed. Cir. 1985) ("Our function is to apply, in each case, § 103 as written to the facts of disputed issues . . . .").

Indeed, in *KSR* this Court expressly rejected as inconsistent with its precedent the application of "mandatory formulas" to determine obviousness. But that is precisely what the Federal Circuit has done here: it has created a mandatory two-step formula that *must* be applied in chemical cases because chemistry is, in the Federal Circuit's view, less predictable than engineering, physics, computing, or anything else. That mandatory, two-step test artificially "limits the obviousness inquiry." *KSR*, 550 U.S. at 419.

Even before *KSR*, it was well accepted that a single obviousness inquiry applies to patents irrespective of subject matter or field of endeavor. As the predecessor to the Federal Circuit recognized, "[t]he problem of 'obviousness' under section 103 in determining the patentability of new and useful chemical compounds . . . is not really a problem in chemistry or pharmacology or in any other related field of science such as biology, biochemistry, pharmacodynamics, ecology, or others yet to be conceived. *It is a problem of patent law*." *In re Papesch*, 315 F.2d 381, 386 (CCPA 1963) (emphasis added) (quoted in *In re Kubin*, 561 F.3d 1351, 1361 (Fed. Cir. 2009)). Similarly, this Court has warned that "the meaning of words in a statute cannot change with the statute's application." *United States* v. *Santos*, 553 U.S. 507, 522 (2008). The "lead compound" test, however, assumes that Section 103(a) means one thing with respect to chemical compositions of

matter and another thing with respect to everything else.[4]

Congress knows full well how to create special rules for certain categories of patents. For example, Section 103(b) sets forth a special obviousness rule for patents on "biotechnological process[es]."[5] But Congress created no such special obviousness rule for chemical compositions. It is not the task of the judiciary to invent special, rigid rules where Congress has created none.

Even if the Federal Circuit were correct that the chemical arts are less predictable than all others, that fact would be no reason to limit the reach of

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[4] The Federal Circuit's artificial bifurcation of "chemical" and "nonchemical" patents will surely generate confusion as to what in fact qualifies as a "chemical" patent subject to the insurmountable "lead compound" test. For example, engineers make computer chips using various chemical engineering techniques (such as depositing silicon onto a chip). Is the invention electrical because it is a computer chip or chemical because it involves the use of a chemical? What about nanodevices that combine "chemical" and "nonchemical" materials?

[5] Section 103(b) provides:

> (b)(1) Notwithstanding subsection (a), and upon timely election by the applicant for patent to proceed under this subsection, a biotechnological process using or resulting in a composition of matter that is novel under section 102 and nonobvious under subsection (a) of this section shall be considered nonobvious if—
>
> (A) claims to the process and the composition of matter are contained in either the same application for patent or in separate applications having the same effective filing date; and
>
> (B) the composition of matter, and the process at the time it was invented, were owned by the same person or subject to an obligation of assignment to the same person.

KSR or adopt a special test. As a different panel of the Federal Circuit correctly observed, there is no reason to "cabin *KSR* to the 'predictable arts' (as opposed to the 'unpredictable art' of biotechnology)." *In re Kubin*, 561 F.3d at 1360.

By directing the obviousness inquiry to the selection and modification of a single lead compound, moreover, the Federal Circuit runs afoul of Section 103(a)'s focus on whether the differences between the subject matter sought to be patented and the prior are such that the subject matter "*as a whole*" would have been obvious. See page 1, *supra*. By its plain terms, then, Section 103(a) requires a holistic view of the patented subject matter, *not* an inquiry structured by a narrow, two-step, sequential "lead compound" test.

In applying the "lead compound" test, then, the Federal Circuit has established a different—and much higher—bar for showing the obviousness of chemical compositions than for all other patents. As explained below, this case illustrates how the court's application of that higher bar causes it to arrive at the wrong result.

B. The "Lead Compound" Test Resurrects An Even More Inflexible Variation Of The Rigid "Teaching, Suggestion, or Motivation" Test Rejected By *KSR* And Leaves No Room For "Obvious To Try" Arguments

The "lead compound" test is not only an impermissible "mandatory formula" for determining obviousness. It also improperly requires courts to apply an even more narrow and inflexible variant of

the "teaching, suggestion, or motivation" ("TSM") test rejected by this Court in *KSR*. Equally problematic, the "lead compound" rule allows courts to reject challenges to "inventions" that, as here, were "obvious to try"—again, in direct conflict with this Court's clear teaching in *KSR*.

In *KSR*, this Court acknowledged that the TSM test could provide a "helpful insight[]," but rejected the Federal Circuit's transformation of that general insight into a "rigid rule" that applies to—and must be satisfied in—all patent cases. *KSR*, 550 U.S. at 419. The "lead compound" test, however, resurrects an even more inflexible variant of the rigid TSM test squarely rejected in *KSR*. And it does so not once, but *twice*: the court's rule requires a specific motivation to select the lead compound in the first place, and then a specific reason to modify that lead compound in a particular manner. If one rigid TSM test runs afoul of *KSR*, then surely so does a two-step, formalistic TSM test that requires two TSM hurdles to be cleared rather than one.

This case presents a clear illustration of the inflexibility of the "lead compound" test and its incompatibility with the "common sense" that this Court invoked in *KSR*, 550 U.S. at 420. The Federal Circuit rejected the obviousness challenge here even while acknowledging that a PHOSITA "would have had reasons—specifically, design need *and* market demand—to create an FDA-approved liquid nasal composition that delivers salmon calcitonin." App., *infra*, 18a-19a (emphasis added). Thus, the Federal Circuit rejected an obviousness challenge even while admitting that there *was* a "teaching, suggestion, or motivation" to copy the active ingredient in

Miacalcin® and even though respondents had designed Fortical® as a deliberate imitation of Miacalcin®. The Federal Circuit reached that result because the narrow and specialized "motivation" demanded under step two of the "lead compound" test—a motivation to make a *particular* modification—assertedly was missing.

KSR recognized that, even without a specific teaching, motivation, or suggestion in the prior art to combine known elements, a particular combination of known elements could be obvious to try. By requiring challengers to show a specific teaching, suggestion, or motivation both to select and to modify a lead compound in a particular way, the Federal Circuit effectively forecloses application of the "obvious to try" test in chemical compound cases. Here again, this case is no exception. As discussed further below, the Federal Circuit did not even consider whether it would be obvious to try using citric acid in a salmon calcitonin composition—even though several prior-art references do exactly that. Consequently, the court erroneously concluded that claim 19 would not have been obvious.

II. The Question Presented Is Important and Recurring

This case raises a significant issue of federal law that arises with substantial regularity in patent litigation. Obviousness is a frequently invoked challenge (and defense to infringement actions) in patent cases. See Michelle Ernst, *Reforming The Non-Obviousness Judicial Inquiry*, 28 CARDOZO ARTS & ENT. L.J. 663, 665 (2011) (discussing empirical data showing that "[n]on-obviousness is an

overwhelmingly prominent area in patent litigation"). Moreover, in recent years, the Federal Circuit has issued a large number of published decisions in cases involving obviousness challenges to pharmaceutical patents.[6] Many of these have involved application of the "lead compound" test.[7]

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[6] See, *e.g., Genetics Institute, LLC* v. *Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291 (Fed. Cir. 2011); *Daiichi Sankyo Co.* v. *Matrix Labs., Ltd.*, 619 F.3d 1346 (Fed. Cir. 2010); *Eli Lilly & Co.* v. *Teva Pharmaceuticals USA, Inc.*, 619 F.3d 1329 (Fed. Cir. 2010); *King Pharmaceuticals, Inc.* v. *Eon Labs, Inc.*, 616 F.3d 1267 (Fed. Cir. 2010); *Bayer Schering Pharma AG* v. *Barr Labs., Inc.*, 575 F.3d 1341, 1346-50 (Fed. Cir. 2009); *Procter & Gamble Co.* v. *Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 994-98 (Fed. Cir. 2009); *In re Kubin*, 561 F.3d 1351, 1358-61 (Fed. Cir. 2009); *Ortho-McNeil Pharmaceutical, Inc.* v. *Mylan Labs., Inc.*, 520 F.3d 1358, 1363-65 (Fed. Cir. 2008); *Abbott Labs.* v. *Sandoz, Inc.*, 544 F.3d 1341, 1350-51 (Fed. Cir. 2009); *Astrazeneca AB* v. *Apotex Corp.*, 536 F.3d 1361, 1379-81 (Fed. Cir. 2008); *Eisai Co.* v. *Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356-59 (Fed. Cir. 2008); *Aventis Pharma Deutschland GmbH* v. *Lupin, Ltd.*, 499 F.3d 1293, 1300-03 (Fed. Cir. 2007); *Takeda Chem. Indus., Ltd.* v. *Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-63 (Fed. Cir. 2007); *Pfizer, Inc.* v. *Apotex, Inc.*, 480 F.3d 1348, 1358-69 (Fed. Cir. 2007); *Alza Corp.* v. *Mylan Labs., Inc.*, 464 F.3d 1286, 1289-95 (Fed. Cir. 2006).

[7] See, *e.g., Daiichi Sankyo Co.,* 619 F.3d at 1352-57; *Altana Pharma AG* v. *Teva Pharmaceuticals USA, Inc.*, 566 F.3d 999, 1006-09 (Fed. Cir. 2009); *Procter & Gamble Co.*, 566 F.3d at 994-95; *Sanofi-Synthelabo* v. *Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008); *Takeda Chem. Indus., Ltd.* v. *Mylan Labs. Inc.*, 549 F.3d 1381, 1385-88 (Fed. Cir. 2008); *Eisai Co.*, 533 F.3d at 1359; *Ortho-McNeil Pharmaceutical, Inc.*, 520 F.3d at 1364; *Takeda Chem. Indus.*, 492 F.3d at 1356-63; *Eli Lilly & Co.* v. *Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1378-80 (Fed. Cir. 2006); *Yamanouchi Pharmaceutical Co., Ltd.* v. *Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1344-55 (Fed. Cir. 2000).

The real-world importance of the question presented cannot be seriously disputed. This Court has repeatedly warned that granting patents on trivial advances over the prior art would "stifle, rather than promote, the progress of the useful arts." *KSR*, 550 U.S. at 427; see also *Bonito Boats Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 143, 148 (1989). By applying a different—and higher—threshold for showing obviousness of chemical compositions, the Federal Circuit makes it dramatically more difficult to invalidate chemical patents. That overly strict interpretation of Section 103(a) as applied only to chemical cases results in more patents on marginal developments over the prior art. Indeed, that perverse consequence is well illustrated by this case, where the patent-in-suit merely sought to piggyback on an already approved drug.

This is a recurring problem. The PTO awards thousands of drug patents each year. See U.S. Patent and Trademark Office, Patenting By Geographic Region (State and Country), Breakout By Technology Class, available at http://www.uspto.gov/web/offices/ac/ido/oeip/taf/clsstc/allstccl_gd.htm (listing patents, although not limited to those patents relating to chemical compositions of matter). Applying the lead compound test, however, the Federal Circuit has found nonobviousness in *every* chemical compound case since *KSR*—in marked contrast to pharmaceutical method-of-treatment cases, where the Federal Circuit has invalidated patents as obvious in a majority of cases. Indeed, since the enactment of Hatch-Waxman in 1984, the Federal Circuit has *never* found a single new-chemical-compound claim to be obvious. The Federal Circuit's *de facto* conferral of invulnerability

on such patents has delayed market entry of cost-saving generic drugs.

Congress's goal, embodied in the Hatch-Waxman Act, was to promote the widespread availability of low-cost generic drugs. See pages 4-6, *supra*. With respect to patents on chemical compounds, that congressional objective is best served by limiting patents to truly innovative drugs. But the "lead compound" test thwarts that purpose.

The impossibly high "lead compound" standard also infects decisionmaking at the PTO. The PTO issued Guidelines in 2010, which incorporate the "lead compound" test. Examination Guidelines Update: Developments in the Obviousness Inquiry After *KSR v. Teleflex*, 75 Fed. Reg. 53,643, 53,651 (Sept. 1, 2010). The rigidity that the Federal Circuit has improperly reintroduced, therefore, will have effects even on patents that never make it into litigation.

Moreover, the "paper NDA" process is specifically intended to streamline the application process for drugs that are modeled on an already approved drug. That procedure gets cheaper medications to consumers faster. Often a generic drug company will file a paper NDA rather than an ANDA so that it can "design around" (and thus avoid infringing) the patent associated with the reference drug. That is exactly what happened here, with one crucial exception: Instead of marketing a generic version of Miacalcin®, Unigene patented its own copy of Miacalcin®. Thus, instead of making a generic drug available to the public at lower cost, Unigene retained a monopoly on Fortical®—artificially elevating the cost to the public (and to the government, which purchases drugs for

Medicare beneficiaries, veterans, members of the military, and others) for years to come.[8]

The Federal Circuit's decision, by providing an easy means for pharmaceutical patentholders to extend monopolies that no longer serve any social purpose, will if left uncorrected contribute to the needless escalation of already soaring health-care costs. Studies have shown that the high cost of drugs can force consumers to skip needed doses. 149 Cong. Rec. H7531, H7533 (daily ed. July 24, 2003); John D. Piette et al., *Cost-Related Medication Underuse Among Chronically Ill Adults: the Treatments People Forgo, How Often, and Who Is at Risk*, 94 AM. J. PUB. HEALTH 1782 (2004). The importance of ensuring that marginal advances in any field are not granted the extraordinary privilege of the patent monopoly is magnified with respect to pharmaceutical compositions, which have significant consequences for human health.

III. The Decision Below Is Erroneous

As explained above, the Federal Circuit's "lead compound" test creates a higher threshold for proving obviousness of patents on chemical compounds and impermissibly narrows the scope of the obviousness inquiry. The court applied the "lead compound" test in this case even though the patent-in-suit involves a new *formulation* of an existing

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[8] Total expenditures on prescription drugs reached nearly a quarter of a trillion dollars in 2009, with the federal government as the single largest purchaser of such drugs. See U.S. Dep't of Health & Human Servs., Expanding the Use of Generic Drugs, APSE Issue Brief, at 6 (Dec. 1, 2010), available at http://aspe.hhs.gov/sp/reports/2010/GenericDrugs/ib.pdf.

chemical compound, rather than a new chemical compound itself. App., *infra*, 18a-23a. As a result of that cramped and flawed approach, the Federal Circuit reached the wrong result in this case.

All that Unigene did here was attempt to make a product as similar to Miacalcin® as possible without actually *being* Miacalcin®; that way, Unigene could take advantage of the "paper NDA" approval process reserved for such "copycat" drugs. The narrow approach that the Federal Circuit takes toward the obviousness inquiry in chemical-composition cases therefore led it to conclude erroneously that a PHOSITA would not have been motivated simply to substitute one inactive ingredient in Miacalcin® with the inactive ingredients in claim 19.

The nub of the Federal Circuit's decision was that it would not have been obvious to use 20 mM citric acid, rather than BZK, as an absorption enhancer in a liquid nasal salmon calcitonin solution containing the exact same active ingredient as Miacalcin®. In reaching that conclusion, however, the court of appeals failed to consider whether it would have been *obvious to try* citric acid for that purpose. And the prior-art references cited by the court show that it would indeed have been obvious to try this: the '014 patent, for example, teaches that citric acid increased the bioavailability of salmon calcitonin; the '116 patent lists citric acid as one of 50 agents that could increase absorption of salmon calcitonin in a liquid formulation; and the '315 patent describes the use of citric acid in a liquid nasal formulation containing salmon calcitonin in the exact same concentration claimed here.

The Federal Circuit quibbled with some minor differences between the use of citric acid in each of those references *individually* and the use of citric acid in claim 19. But, because the court applied the rigid "lead compound" test, it failed to consider those references *collectively*. See *KSR*, 550 U.S. at 415, 418 (requiring a "broad inquiry" into the "inter-related teachings of multiple patents"). "Common sense teaches . . . that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id*. at 420. Fitting the teachings of multiple patents together like pieces of a puzzle is exactly what Dr. Stern did—with, as the Federal Circuit admitted (App., *infra*, 18a-19a), ample motivation to do so. The prior references taken together made it obvious for a PHOSITA to try using citric acid to increase bioavailability of salmon calcitonin.

Applying the "lead compound" test, however, the Federal Circuit reached the opposite conclusion—and reached the same conclusion it has reached in *every* case since *KSR* in which a chemical-compound claim has been challenged as obvious. The use of rigid tests to reject all such challenges should not be allowed to continue. This case provides a suitable vehicle for reminding the Federal Circuit of the lessons of *KSR* and opening the door for well-founded obviousness challenges to increase the availability of low-cost drugs when no valid innovative purpose is served by upholding the patent monopoly.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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