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IN THE

# Supreme Court of the United States

MYLAN INC., MYLAN LABORATORIES INC., MYLAN PHARMACEUTICALS INC. AND MATRIX LABORATORIES LTD.,

*Petitioners,*

*v.*

DAIICHI SANKYO COMPANY, LTD. AND DAIICHI SANKYO, 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

Whether, contrary to this Court's decision in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), the Federal Circuit has erred in applying a "lead compound test" as the exclusive standard for determining whether a patent claim directed to a new chemical compound is "obvious" and therefore invalid under 35 U.S.C. § 103(a).

## PARTIES TO THE PROCEEDINGS AND CORPORATE DISCLOSURE STATEMENT

Petitioner Mylan Inc., formerly known as Mylan Laboratories Inc., is a publicly held corporation. Mylan Pharmaceuticals Inc. is a wholly owned subsidiary of Mylan Inc. No other parent corporations or publicly held companies own 10% or more of the stock of Mylan Inc.

Matrix Laboratories Ltd. is a privately held corporation. MP Laboratories (Mauritius) Ltd. owns a majority of stock of Matrix Laboratories Ltd., and is itself a wholly owned subsidiary of Mylan Inc. No other parent corporation or publicly held company owns 10% or more of the stock of Matrix Laboratories Ltd.

## TABLE OF CONTENTS

## TABLE OF AUTHORITIES

### Cases

**Statutes**

**Other Authorities**

## TABLE OF APPENDICES

## PETITION FOR A WRIT OF CERTIORARI

Petitioners (collectively, "Mylan") respectfully petition for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit.

## OPINIONS AND ORDERS BELOW

The opinion of the court of appeals (App. 1a-24a.) is reported at 619 F.3d 1346 (Fed. Cir. 2010). The opinion of the district court (App. 25a-84a.) is reported at 670 F. Supp. 2d 359 (D.N.J. 2009).

## JURISDICTION

This Court has jurisdiction under 28 U.S.C. § 1254(1). The court of appeals entered judgment on September 9, 2010. No petition for rehearing was filed. The court of appeals had jurisdiction of Petitioners' appeal under 28 U.S.C. § 1295(a)(1). The district court had jurisdiction of Respondents' patent infringement claim under 28 U.S.C. § 1338(a).

## STATUTORY PROVISION INVOLVED

This case concerns the standard of patentability under 35 U.S.C. § 103(a), which provides:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, 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 OF THE CASE

Diabetes. Epilepsy. Osteoporosis. Hypertension. For each of these chronic illnesses, a specific name-brand drug offers some aspect of treatment. Yet in each case, no generic equivalent exists because a patent on the branded drug claims the active ingredient as a new chemical compound.

This case presents an important issue about a legal standard applied in a significant subset of patent cases brought under the Hatch-Waxman Act.[1] The Hatch-Waxman Act established a regulatory framework by which a generic drug manufacturer can file an Abbreviated New Drug Application ("ANDA") to seek approval from the FDA to sell a generic version of an already approved drug. Most Hatch-Waxman patent cases arise when a generic drug manufacturer challenges a patent listed for an existing branded drug as being invalid for, among other reasons, obviousness. A patent claim is obvious under 35 U.S.C. § 103 if the subject matter of the claim would have been a predictable variation over the prior art by a person with ordinary skill in the relevant field. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

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[1] The Hatch-Waxman Act is formally known as the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355 and 35 U.S.C. § 271).

A troubling pattern has emerged in the Federal Circuit's Hatch-Waxman Act cases in which that court has rejected every structural obviousness challenge to a patent claiming a new chemical compound *since Congress passed the Act in 1984.* [2] This long-standing pattern has crystallized more recently with the Federal Circuit's consistent application of a "lead compound" test as the exclusive, rigid standard for determining obviousness of chemical compound patent claims. Like the teaching, suggestion, or motivation ("TSM") test that *KSR* rejected as the sole test for obviousness, the lead compound test requires a challenger to establish that one of ordinary skill in the art would have been motivated (1) to select a lead compound from the prior art to develop and (2) to make the necessary modifications to the prior art lead compound to arrive at the claimed compound. *See, e.g., Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). This analysis was not initially intended to be a specialized obviousness test, but over time it became canonized by mechanical application in the district courts and the Federal Circuit. As applied after *KSR*, the lead compound test now stands in defiance of this Court's holding in *KSR* that the question of obviousness should be addressed with an expansive and flexible approach.

The Federal Circuit is imposing an obviousness standard for new chemical compounds that is

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[2] A "chemical compound" is "a substance formed from two or more elements chemically united in fixed proportions." Compact Oxford English Dictionary (April 2010).

analytically inflexible and practically impossible to meet. This standard indicates a disconnect between how a chemist creates new compounds and the obviousness standard used by the courts and the Patent and Trademark Office ("PTO") to determine whether that chemist's work was truly non-obvious and, thus, patent-worthy. If the standard for obviousness in these cases is overly rigid and impracticable, then the validity of every patent claim reciting the active ingredient of a branded drug will be unjustifiably unassailable under § 103(a).

Without this important defense to patent infringement claims, approval of generic equivalents of branded drugs is being delayed in cases where it should not. As a result, consumers are paying more for drugs protected by monopolies that may never have survived the scrutiny of patent law had the correct legal standard been applied. This reality contradicts the Hatch-Waxman Act's objective, evident from the official title referring to "price competition," of spurring a robust generic drug market by enforcing only valid patents on truly innovative drugs and discarding invalid patents on obvious ones. *See supra* n.1; *see also* 130 Cong. Rec. 24427 (Sept. 6, 1984) (statement of Rep. Waxman) ("A patent is a monopoly . . . as a matter of public policy we, under the patent law, give that protection to the person who has put money into research and development for an innovative new product. But at some point public policy calls for the free market system competition which will bring about the result of a lower price for the consumer. That is the purpose of the legislation.").

Instead of using the lead compound test, chemical compound patent claims should be evaluated on a case-by-case basis, with less focus on "predictability" *per se* of the claimed compound and greater focus on whether the claimed compound was "obvious to try" to a chemist of ordinary skill. Such an approach is consistent with the flexible analysis *KSR* requires, and it is especially vital in the chemical arts where, to chemists of ordinary skill, structure and activity may not be entirely predictable, but the claimed structure is obvious to try in a methodical trial-and-error process.

1. The chemical compound at issue in this case is *olmesartan medoxomil, which is used alone or in* combination with other drugs to treat hypertension. Olmesartan is in a class of medications known as angiotensin receptor blockers ("ARBs") and, more specifically, olmesartan is an angiotensin II ("AII") receptor antagonist. It allows blood to flow more easily through arteries by blocking certain substances from binding to the surfaces of cells. Such binding is why arteries narrow, constricting blood flow and increasing blood pressure.

2. Petitioner Mylan filed an ANDA for approval to engage in the commercial manufacture, use or sale of 5mg, 20mg, and 40mg tablets of olmesartan medoxomil, a generic equivalent of the branded drug sold by Daiichi Sankyo as Benicar®. Mylan later filed additional ANDAs on two separate combinations of olmesartan medoxomil with other compounds used to treat hypertension: a combination with hydrochloro-thiazide ("HCTZ") (sold as Benicar HCT®) and a combination with amlodipine besylate (sold as Azor®). For each ANDA, Mylan filed a

Hatch-Waxman Paragraph IV certification that its generic products would not infringe any valid claim of U.S. Patent No. 5,616,599 (the "'599 patent"), which is owned by Daiichi Sankyo. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

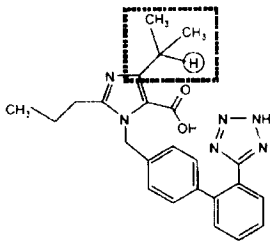
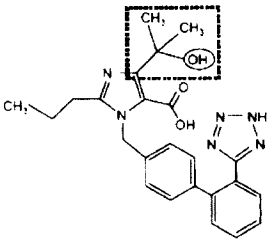
3. Pursuant to the Hatch-Waxman Act, Daiichi Sankyo filed three patent infringement suits in the United States District Court for the District of New Jersey. The three actions were consolidated and the parties stipulated that Mylan's olmesartan medoxomil products would infringe claim 13 of the '599 patent. The only issue before the court was whether claim 13 was obvious over prior art that included discoveries made by DuPont, which were in turn developed based on earlier discoveries made by the Japanese pharmaceutical company Takeda.

In the late 1970s, Takeda discovered the first AII receptor blocker. The Takeda compounds had little therapeutic value, however, as they did not work when administered orally. In 1982, DuPont used three of the Takeda compounds as models for an ARB research program. The successful result was losartan, sold under the brand name Cozaar® and the first orally active ARB to be approved by the FDA and marketed.

Losartan was disclosed by DuPont's prior art '069 patent, as were more than 400 structurally related ARBs. Subsequently, DuPont discovered ARBs with a greater oral activity than losartan. A group of six particularly active compounds were disclosed in DuPont's prior art '902 patent.

At the core of the Takeda lead compound, losartan, and later second-generation ARB compounds, was an imidazole ring. Imidazole is an

organic compound with the formula $C_3H_4N_2$. It is a common structural core used in pharmaceutical compounds. As shown below, olmesartan, the compound claimed in Daiichi Sankyo's '599 patent in suit, differs from one of DuPont's '902 compounds by *a single atom*. While olmesartan contained a hydroxyl group (–OH) at the 4-position of the imidazole ring, the '902 compound had a hydrogen atom (H) at that position:

| '902 Example 6 | Olmesartan |
|---|---|
|  |  |

The only other modification Daiichi Sankyo made was the addition of a medoxomil group at the 5-position of the ring. Medoxomil has been used by medicinal chemists to improve oral absorption of similar compounds well before the priority date of the '599 patent.

Following a ten-day bench trial, the district court held that, notwithstanding the minor difference between olmesartan and the prior art, Mylan failed to prove that olmesartan medoxomil was obvious in light of the prior art. A week later, the district court entered its judgment and issued an injunction prohibiting approval of Mylan's ANDA until the expiration of the '599 patent in 2016. Applying the rigid lead compound test, the district court concluded that although the Daiichi Sankyo patent applicants

admitted that the improved ARBs described in DuPont's '902 patent were the closest prior art to olmesartan, Mylan failed to show by clear and convincing evidence that a person of ordinary skill in the art of medicinal chemistry would have been motivated to select the prior art '902 compounds as lead compounds for further investigation. The court further determined that if the prior art '902 compounds were selected as lead compounds, one of ordinary skill in the art would not have been motivated to modify the lead compounds to arrive at the claimed compound because the prior art taught away from this. Thus, the court concluded that Mylan failed to establish *prima facie* obviousness.

Having already concluded that neither motivational step of the lead compound test had been satisfied, the district court went on to make the following additional findings: (a) although the only structural difference between the compounds is that the claimed compound includes an –OH group where the prior art compound has an –H atom and the addition of the well-known prodrug medoxomil, olmesartan medoxomil was not structurally similar to the '902 compound; (b) despite extensive prior use of medoxomil as a prodrug in several drugs treating hypertension and Daiichi Sankyo's admission of this fact to the PTO, the addition of the medoxomil prodrug to the olmesartan molecule was not obvious; (c) a person of ordinary skill in the art of medicinal chemistry would not have had a reasonable expectation of obtaining olmesartan medoxomil's increased oral absorption; and (d) "secondary considerations," particularly unexpected results and commercial success, overcame any *prima facie* case of obviousness. (App. 71a-73a.)

4. On appeal, the Federal Circuit affirmed the district court's decision that Mylan had failed to establish a *prima facie* case of obviousness under the lead compound test. (App. 24a.)

5. According to the court of appeals, two of its earlier decisions, *Takeda Chem. Indus. Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), and *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369 (Fed. Cir. 2006), illustrated that "it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds" and that the obviousness analysis "requires the challenger to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art." (App. 17a-18a.) The Federal Circuit declined to review the district court's additional findings.[3] (App. 24a.)

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[3] The district court's additional findings were made in the context of its not having found a *prima facie* case of obviousness as a result of its erroneous lead compound approach. Evaluation of each of these additional findings depends upon the strength of the *prima facie* case on obviousness. If this Court agrees with Petitioners that the Federal Circuit erred in applying a lead compound test instead of taking the flexible approach mandated in *KSR*, then the proper result would be to vacate the Federal Circuit decision and remand for consideration of all facets of the obviousness question in the proper legal context.

## REASONS FOR GRANTING THE WRIT

### I. Like the TSM Test that *KSR* Rejected, the Lead Compound Test Is Too Rigid and Sets an Impossibly High Standard for Obviousness in Chemical Compound Cases.

Patent claims asserted in Hatch-Waxman litigation are generally directed to one of a few categories of subject matter, such as new chemical compounds, specific configurations of known compounds (i.e., stereoisomers[4]), pharmaceutical formulations of known compounds, methods of using or preparing a compound, and methods of treating a medical condition. How an asserted claim is drafted determines the category into which it falls. Within these categories, new chemical compound claims are peculiar in that when they are challenged as being invalid for obviousness under 35 U.S.C. § 103, Federal Circuit case law requires that they be evaluated under a special obviousness analysis not applicable to any of the other categories: the "lead compound" test.

To establish a claimed chemical compound as obvious over the prior art under the lead compound test, a challenger must prove that one of ordinary skill in the art would have chosen the closest prior art as a "lead compound" and that the modification of the

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[4] Stereoisomers are compounds that contain the same constituent atoms and the same bonding between those atoms but have different spatial arrangements. *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1265 (Fed. Cir. 2007).

lead compound to arrive at the claimed compound was obvious. Like the rigid TSM test that *KSR* rejected as the sole test of obviousness, the lead compound test requires a challenger to establish that one of ordinary skill in the art would have been motivated in two specific ways: (1) to select the lead compound and (2) to modify the lead compound to arrive at the claimed compound.[5] The two parts are not alternatives; a challenger must satisfy both prongs to establish a *prima facie* case of obviousness.

This Court explained in *KSR* that obviousness in *all* patent cases should be evaluated by a flexible test. 550 U.S. at 415, 419 (explaining that throughout the Court's engagement with the question of obviousness, its decisions have set forth "an expansive and flexible approach" effected by "broad inquiry" rather than "rigid and mandatory formulas" and particularized tests). The Federal Circuit has disregarded this guidance and continues to apply the same lead compound test to all new chemical compound claims as an inflexible rule. *See, e.g.*, *Eisai*, 533 F.3d at 1359 ("[P]ost-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.").

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[5] *See, e.g.*, *Takeda*, 492 F.3d at 1357 (affirming nonobviousness where the district court determined that the challenger "failed to adduce evidence that compound b would have been selected as the lead compound and, even if that preliminary showing had been made, it failed to show that there existed a reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the claimed compounds").

Applying the lead compound test rigidly, the Federal Circuit has found nonobviousness in *each and every* chemical compound patent case since *KSR*. In contrast, for example, the court has found two out of three pharmaceutical method-of-treatment patents obvious over the same time period. As the following table demonstrates, the Federal Circuit is effectively applying a much higher standard to chemical compounds than it does to other inventions, even within the chemical arts.[6]

| Category | Case / Compound | Conclusion |
|---|---|---|
| Chemical Compound | *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007) / pioglitazone (to treat type II diabetes) | Not obvious |
| Chemical Compound | *Eisai Co. Ltd. v. Dr. Reddy's Labs., Inc.*, 533 F.3d 1353 (Fed. Cir. 2008) / rabeprazole (to treat ulcers) | Not obvious |
| Chemical Compound | *Ortho-McNeil Pharma., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358 (Fed. Cir. 2008) / topiramate (to | Not obvious |

[6] The table does not include *Altana Pharma AG v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 999 (Fed. Cir. 2009), a chemical compound case in which the Federal Circuit affirmed the district court's denial of a preliminary injunction, because the Federal Circuit did not rule on the merits of the defense.

| | | |
|---|---|---|
| | treat seizures) | |
| Chemical Compound | *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009) / risedronate (to treat osteoporosis) | Not obvious |
| Chemical Compound | *Daiichi Sankyo v. Matrix Labs.*, 619 F.3d 1346 (Fed. Cir. 2010) / olmesartan (to treat hypertension) | Not obvious |
| ***Compared With*** | | |
| Method of Treatment | *Daiichi Sankyo v. Apotex*, 501 F. 3d 1254 (Fed. Cir. 2007) | Obvious |
| Method of Treatment | *PharmaStem Therapeutics v. Viacell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007) | Obvious |
| Method of Treatment | *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 619 F.3d 1329 (Fed. Cir. 2010) | Not obvious |

In *Takeda*, the Federal Circuit affirmed the district court's nonobviousness determination. 492 F.3d at 1359. The Federal Circuit stated that its pre-*KSR* precedent regarding structural similarity required defendants to establish that the "prior art would have *suggested* making the *specific* molecular modifications necessary to achieve the claimed invention," *id.* at 1356 (emphasis added), or that there was "adequate support in the prior art" of some "*reason* or *motivation*" to make the claimed

compound, *id.* (emphasis added). Although this Court rejected the "rigid and mandatory" TSM formula in *KSR*, the Federal Circuit reasoned that this precedent was consistent with *KSR* and further stated that "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 of a new claimed compound." *Id.* at 1357. The Federal Circuit specifically rejected defendant's arguments that a nonobviousness determination was contrary to *KSR* because the identified lead compound ("compound b") was within "the objective reach of the claim" and the evidence demonstrated that using the techniques of homologation and ring-walking would have been "obvious to try." *Id.* at 1359. The court reasoned that the "obvious to try" argument failed because the prior art did not "identify predictable solutions for antidiabetic treatment," that the choice of compound b as a lead compound was not clear, and certain negative properties of compound b would have taught away from its choice as a lead compound. *Id.*

In *Eisai*, Teva argued that the claimed compound was obvious over the combination of three references that disclosed prior art compounds lansoprazole and omeprazole. 533 F.3d at 1357. Teva asserted that one of ordinary skill in the art would have been motivated to start with lansoprazole as a lead compound because it was structurally identical to the claimed compound but for one substituent on its pyridine ring. *Id.* Citing *Takeda*, the Federal Circuit explained that this Court's analysis in *KSR* relied on several assumptions regarding the prior art landscape and that "*KSR* presupposes that the record

up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound." *Id.* at 1359. The court found that the record showed "no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature . . . that gave [it its] advantageous property" of being lipophilic. *Id.* at 1358.

In *Ortho-McNeil*, the Federal Circuit determined that there was nothing in the record showing that (i) an ordinarily skilled artisan who sought to develop the same type of anticonvulsant as the claimed compound would have started with the prior art compound the inventor started with, (ii) the artisan would have had "some reason to select (among several unpredictable alternatives) the exact route that produced" the claimed compound as an intermediate, or (iii) the artisan would have had any reason to stop at the intermediate and test it for properties far afield from the purpose for the development (i.e., epilepsy rather than diabetes). 520 F.3d at 1364.

In *Procter & Gamble*, the Federal Circuit determined that even if the identified lead compound was selected as a lead compound, the evidence did not establish that it would have been obvious to a person of ordinary skill in the art to modify it to create the claimed compound. 566 F.3d at 995. According to the court, the properties of bisphosphonates, which included both the lead compound and the claimed compound, could not be anticipated based on their structure. *Id.* at 996. The court supported this "unpredictability" finding by noting that plaintiff had synthesized three structural isomers of the claimed

compound—the lead compound, the claimed compound, and a third compound—and found the third compound "was not active in inhibiting bone resorption despite its close relationship with potent compounds." *Id.* In view of this unpredictability and "an insufficient showing that a person of ordinary skill in the art would have had a 'reasonable expectation of success' in synthesizing and testing the claimed compound, the Federal Circuit determined "there [wa]s no credible evidence that the structural modification was routine" and, therefore, the claimed compound was not obvious. *Id.*

In this case, *Daiichi Sankyo*, the Federal Circuit determined that Mylan failed to show that one of ordinary skill in the art would have been motivated to select the ARBs disclosed in the DuPont '902 patent as lead compounds and, even if the '902 ARBs had been selected as lead compounds, Mylan failed to show that a skilled artisan would have been motivated to modify them to synthesize the claimed compound. (App. 15a.) Specifically, the Federal Circuit affirmed the district court's finding that even though the '902 ARBs "'exhibit[ed] remarkable and unexpected potency as antihypertensives,'" the prior art included even more potent antihypertensives such that a medicinal chemist of ordinary skill would not have been motivated to choose the '902 ARBs over the more potent compounds. (App. 16a.) (quoting *Daiichi Sankyo Co., Ltd. v. Mylan Pharms. Inc.*, 670 F. Supp. 2d 359, 376 (D.N.J. 2009)). The Federal Circuit reasoned that "[p]otent and promising activity in the prior art trumps mere structural relationships." (App. 17a.)

Regarding the motivation to modify the lead compounds, the Federal Circuit found that even if the medicinal chemist of ordinary skill chose the '902 ARBs as lead compounds, the prior art taught away from the use of a hydrophilic substitute at the 4-position of the imidazole ring because, among other reasons, "[t]he few compounds [in the prior art] with hydrophilic groups at the 4-position are drowned out by the sea of 4-lipophilic compounds." (App. 19a.) Further, the court found, the '902 ARBs would be attractive as lead compounds specifically because they included lipophilic alkyl groups at the 4-position and "'a person of ordinary skill in the art would not select the '902 patent compounds as leads only to disregard one of their distinguishing characteristics.'" (App. 23a (quoting *Daiichi Sankyo*, 670 F. Supp. 2d at 379).) Lastly, the Federal Circuit stated that even if the prior art did not teach away from the hydrophilic group at the 4-position, the prior art "simply does not provide a reason to make such a modification." (App. 23a.)

Each of these cases is substantively unique, and there is no compelling reason to apply a single, inflexible test to them. In spite of *KSR*'s rejection of such an approach (which is analogous to the TSM test), the Federal Circuit continues to apply the same flawed lead compound test in all its post-*KSR* chemical compound cases. *KSR*, 550 U.S. at 419 ("The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents.").

## II. Rigid Application of the Lead Compound Test Undermines Fundamental Policies of the Patent and Drug Laws.

The underlying goal of the Hatch-Waxman Act is to preserve incentives to engage in research and development while promoting the wider availability of generic drugs.[7] In cases involving chemical compound patents, this policy is achieved when a finding of nonobviousness is reserved for truly innovative discoveries, as opposed to incremental developments over the prior art. Yet the opposite is occurring, indicating a trend whereby courts are overly reluctant to reach a conclusion of obviousness in chemical compound cases, regardless of whether

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[7] *Teva Pharms. USA v. Pfizer, Inc.*, 405 F.3d 990, 995 (Fed. Cir. 2005) ("The [Hatch-Waxman Act] provides an express mechanism for generics to challenge, with declaratory actions, the claim scope or validity of listed patents. Under this statutory scheme, it is court challenges by generic drug companies that limit incumbent overreaching by submitting over-inclusive lists of patents applicable to any given branded formulation."); *see also* Hearing on H.R. 1706 Before the H. Subcomm. on Commerce, Trade, and Consumer Protection, 111th Cong., 10 (Mar. 31, 2009) (statement of Subcomm. Chair Hon. Bobby L. Rush) ("As a carrot to encourage patent challenges, the Hatch-Waxman Act provides the first filer 180 days of exclusivity as the only generic drug permitted on the market, simply enabling a successful generic company challenger to recoup its significant litigation costs. It is this reward that encourages the risk of challenging a patent. If this exclusivity is no longer granted, the result will be the opposite of what this bill intends. Fewer drugs patents will be challenged, and consumers will have to wait much longer until patents expire or litigation come to conclusion before cheaper generic drugs can be made available.").

the claimed compound results from a minor modification to a known compound that, while perhaps not obvious to a lay person, is well within the ability and insight of a chemist of ordinary skill.[8]

This trend contradicts the expansive and flexible approach to evaluating obviousness that this Court required in *KSR*:

> The diversity of inventive pursuits and of modern technology counsels against limiting the analysis [in a formalistic manner]. Granting 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.

550 U.S. at 418; *see also* U.S. Fed. Trade Comm'n, To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy 6 & n.23 (2003), *available at* http://www.ftc.gov/os/2003/10

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[8] *Compare Perfect Web Technologies, Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1328 (Fed. Cir. 2009) (holding a claimed method for managing bulk e-mail distribution to be obvious where there was a "finite number of identified, predictable solutions" and the supposedly inventive step was "obvious to try because there were, at most, two or three predictable solutions at the time for ensuring e-mail delivery.") *with Takeda*, 492 F.3d at 1359 (Fed. Cir. 2007) (rejecting the argument that the claimed compounds were obvious despite the fact that the lead compound fell within the objective reach of the claim and evidence demonstrated that the techniques of homologation (replacing a methyl group with an ethyl group) and ring-walking (moving the ethyl substituent to another position on the ring) would have been "obvious to try" to one ordinarily skilled in the art.).

/innovationrpt.pdf (discussing how a restrictive obviousness standard can result in unwarranted market power that delays competition).[9]

The *quid pro quo* of patent protection is that in exchange for disclosure to the public of a novel and nonobvious invention, the patentee receives exclusive rights to the invention for a limited time. *See* U.S. Const., art. 1, § 8. In the context of this exchange, patentability standards like nonobviousness under 35 U.S.C. § 103 take on heightened significance in drug discovery because an overly strict application of the analyses used to test alleged inventions against these standards results in unchallengeable patents on marginal developments over the prior art that hinder rather than promote the progress of science.

Nowhere is the impact of patent law on the public interest more apparent than in Hatch-Waxman cases. Yet, despite a constitutional mandate that patents be issued only for truly innovative inventions, explicit Congressional intervention to promote a robust generic drug market, and clear Supreme Court precedent requiring flexibility and case-by-case analysis, the Federal Circuit has not found even a single chemical compound claim to be obvious since

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[9] *Accord Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008) ("The methodology of science and the advancement of technology are founded on the investigator's educated application of what is known, to intelligent exploration of what is not known. Each case must be decided in its particular context, including the characteristics of the science or technology, its state of advance, the nature of the known choices, the specificity or generality over the prior art, and the predictability of results in the area of interest.").

enactment of the Hatch-Waxman Act. Meanwhile, the high cost of drugs forces the afflicted to skip needed doses. *See* John D. Piette et. al., *Cost-Related Medication Underuse Among Chronically Ill Adults: the Treatments People Forgo, How Often, and Who Is at Risk*, Am J Public Health (2004).

This trend is further perpetuated by the PTO's adoption of the lead compound analysis in its 2010 PTO Guidelines for patent examiners. Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex, 75 Fed. Reg. 53,643 (Sept. 1, 2010) ("2010 PTO Guidelines"), *available at* http://edocket.access.gpo.gov/2010/pdf/2010-1646.pdf. Although the PTO mentions that six rationales in addition to the TSM test can be used to support an obviousness determination, most of the chemical compound cases appear under the lead compound analysis. Without direction from Congress or this Court to refrain from an overly rigid lead compound analysis, the infection that pervades the courts will continue to spread through the PTO as well.

Finally, although the patent law treatment of chemical compounds may seem to be a technical concept best suited for specialized determination by the PTO and the Federal Circuit, the public and the government ultimately incur the expense of delayed action, and Supreme Court inaction, on this issue. Indeed, when signing the Hatch-Waxman Act into law, President Reagan emphasized "the American people will benefit, because the Federal Government, the largest single consumer of drugs, will be able to purchase generic drugs at significantly lower cost." Remarks on Signing S. 1538 Into Law, 20 Weekly Comp. Pres. Docs. 1349, 1360 (Sept. 24, 1984) (noting

that in 1983 the government spent $2.4 billion on drugs for Medicaid, veterans and military hospitals). Since the passage of the Act, government expenditures on prescription drugs have only increased. *See, e.g.*, Congressional Budget Office, Effects of Using Generic Drugs on Medicare's Prescription Drug Spending vii (2010), *available at* http://www.cbo.gov/ftpdocs/118xx/doc11838/09-15-PrescriptionDrugs.pdf (approximating that, in 2007, $60 billion was spent on drug prescriptions for the Medicare Part D program, of which 30% was filled with branded drugs).

That no patents for drugs claiming chemical compounds have been held invalid for obviousness since the passage of the Act indicates that the policies of the Hatch-Waxman Act are being undermined by the prevailing legal analysis.

## III. The Lead Compound Test Has Been Flawed Since Its Inception and Should Be Replaced with a Flexible, Case-By-Case Basis Analysis.

### a) The lead compound test was an accident.

The lead compound test is the result of an unchecked propagation of error in Federal Circuit case law that only this Court can remedy. The test has origins in (1) a loose statement that was made in *Yamanouchi v. Danbury*, 231 F.3d 1339, 1345 (Fed. Cir. 2000), and implicitly adopted in *Eli Lilly*, 471 F.3d at 1377-79, regarding the selection of a lead compound; and (2) dicta in *Takeda*, 492 F.3d at 1357 that "in cases involving new chemical compounds, it

remains necessary to identify some reason that would have led a chemist to modify a known compound."

The lead compound concept was first discussed in *Yamanouchi* not as a test but as a rejection of an argument made by the defendant to support its theory of obviousness. The *Yamanouchi* opinion explained how each step of defendant's multi-step theory of how a skilled artisan could have used the prior art to arrive at the claimed compound did not work. Beginning its analysis with defendant's first argument that it was obvious to select a certain reference as a lead to make the claimed compound, the court stated: "[a]t the outset, [defendant] did not show the *required motivation for selecting example 44 as a lead compound.*" *Id.* at 1344-45 (emphasis added). The "required motivation" language referred to an argument made by defendant that it would have been obvious to a person ordinarily skilled in the art to take three particular steps to create the claimed compound, the first of which was to select a compound from an earlier patent as a "lead compound."

While not intended to be applied as a firm rule, this statement was cited subsequently by district courts for the proposition that "[d]efendants must establish by clear and convincing evidence that one of ordinary skill in the art would have been motivated to select [the closest prior art compound] as a lead compound." *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F. Supp. 2d 820, 904 (S.D. Ind. 2005). On appeal, the Federal Circuit noted, but did not address, defendants' argument that the district court had erred by erecting a "threshold requirement that defendants establish a teaching or incentive to

treat the closest prior art . . . as a lead compound." 471 F.3d. at 1377. Instead, the Federal Circuit highlighted the similarities between the case before it and *Yamanouchi* because in both situations the "defendants ha[d] not shown that a person ordinarily skilled in this art would have selected [the closest prior art compound] as a lead compound." *Id.* at 1379.

In this manner, although case law never discussed a requisite showing of motivation to select a lead compound, a statement in *Yamanouchi* that was never intended to establish a rule was implicitly adopted by *Eli Lilly* and mistakenly interpreted as doctrine. *See, e.g., Eisai Co., Ltd. v. Teva Pharms. USA, Inc.*, No. 03-civ-9223, 2006 U.S. Dist. LEXIS 73516, at *23 (S.D.N.Y. Oct. 5, 2006); *Takeda Chem. Indus. v. Mylan Labs., Inc.*, 459 F. Supp. 2d 227, 242 (S.D.N.Y. 2006).

b) The lead compound test is rooted in and suspectible to the same misuse as the TSM test.

While *Yamanouchi* shows the lead compound concept was not intended to be a rule, *Takeda* shows that the fundamental problem with its adoption as a rule is that it was rooted in the TSM test that *KSR* just two months prior had warned should only be applied *flexibly*. Discussing *KSR, Takeda* noted that it remained important to identify "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." 492 F.3d at 1356-57 ("As long as the [TSM] test is not applied as a rigid and mandatory formula, that test can provide helpful insight to an obviousness inquiry.") (internal

quotation marks omitted). Although the Federal Circuit reiterated *KSR*'s warning that overly rigid tests are not to be used in an obviousness analysis, the court did not heed the warning in that case or in the chemical compound cases that followed. *See, e.g., Eisai*, 533 F.3d at 1356-57 (citing to *Takeda* for the rule that "[o]bviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound."); *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (citing to *Eisai.* and *Takeda* for the same); *Altana*, 566 F.3d at 1007 (citing *Takeda* and *Yamanouchi* for the same).

Indeed, the analysis the Federal Circuit applied before *Yamanouchi* more appropriately recognized that flexibility is necessary in the chemical arts. In *In re Dillon*, the court of appeals reaffirmed that *prima facie* obviousness in chemical compound cases can be established by demonstrating (1) structural similarity between the claimed and prior art compositions and (2) motivation to make the new composition. 919 F.2d 688, 692-93 (Fed. Cir. 1990). The court cautioned, however, that:

> *Each situation must be considered on its own facts*, but it is not necessary in order to establish a *prima facie* case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from the prior art that the claimed compound

> or composition will have the same or a similar utility as one newly discovered by applicant.

*Id.* (emphasis added) (citation omitted). In short, *Dillon* stressed that it "is not the law" that a *prima facie* obviousness rejection must be supported by a reference showing or suggesting newly discovered properties. *Id.*

c) The lead compound test should be abandoned for a more flexible analysis that focuses less on "predictability" *per se.*

In its post-*KSR* chemical compound cases, the Federal Circuit has used the perceived "unpredictability" of medicinal chemistry to support its underlying rigid application of the lead compound rule. To be sure, *KSR* stressed "predictability" as a theme courts should consider seriously in analyzing obviousness. However, *KSR* was also clear that the perspective from which predictability should be evaluated is always that of the person of ordinary skill in the relevant art. Evaluating obviousness from this perpsective on the facts of each case is the only way to ensure that the appropriate standard of predictability is met.

In fields where those of ordinary skill routinely manage unpredictability, the obviousness analysis should focus less on "predictability" *per se* and more on whether the alleged invention was "obvious to try," another theme stressed by *KSR*. This type of subject matter-sensitive calibration of the obviousness analysis is consistent with the flexible case-by-case analysis *KSR* requires. This type of analysis is especially vital in the chemical arts where, to medicinal chemists of ordinary skill, the result of

combining certain structural features or substituents may not be entirely predictable, but their combination is "obvious to try" in a laboratory where properties of compounds are tested day after day in the methodical trial-and-error process that is the mainstay of chemical synthesis. Predictability is a highly relative term because experience and specialized knowledge often yield inferences that are anticipated in some arts and not in others.

In *KSR*, this Court expressly noted that it was error for the Federal Circuit to conclude that a patent claim cannot be proved obvious merely by showing that it was obvious to try. *KSR*, 550 U.S. at 421. Nonetheless, the Federal Circuit appears to be resistant to the obvious to try rubric and has found it inapplicable in several situations. For example, it has refused to apply it where there are a multitude of ways to solve a problem, where no "reason" exists to make a modification, and where there is no "predictability" of success in a combination. *KSR* expressly contemplated that "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.*

In line with this principle, both the 2007 and 2010 PTO Guidelines list an "obvious to try" analysis as one of six rationales that, per *KSR*, can support a determination of obviousness. 2010 PTO Guidelines, 75 Fed. Reg. 53,643, 53,644. As to when and how this approach should be used, this Court's guidance was that:

> 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.

*KSR*, 550 U.S. at 421 (emphasis added).

Elaborating on the definition of "obvious to try" the PTO Guidelines require a two–part showing that the skilled artisan (1) have chosen "from a finite number of identified, predictable solutions" and (2) did so with "a reasonable prediction of success." PTO Guidelines at 53,644. While the first part of the PTO's description has roots in the "predictable solutions" language used by the Supreme Court in *KSR*, the latter portion of the PTO's description was recently emphasized by the Federal Circuit in *In re Kubin* as indicative of what a skilled artisan would have expected in light over the prior art. 561 F.3d 1351, 1360-61 (Fed. Cir. 2009).

Thus, although last year the Federal Circuit in *Kubin* noted that this Court in *KSR* resurrected the obvious to try rationale, the Federal Circuit still refuses to use the obvious to try defense in chemical compound cases. Instead, the Federal Circuit has exclusively applied the lead compound analysis to such cases because of "unpredictability." The danger of using such an approach is that it ignores the wealth of detail that can potentially separate each case on its facts. And in cases like this case, where there was a well developed record establishing what was routine from the perspective of a medicinal chemist, the finding of nonobviousness was "likely the product not of innovation but of ordinary skill and common sense . . . [where] the fact that a combination

was obvious to try might [have shown] that it was obvious under § 103." *Id.*

## IV. This Case Is An Appropriate Vehicle for Resolving the Question Presented.

This case provides a prime opportunity for this Court to consider whether the lead compound test is inconsistent with *KSR*.

*First*, the lead compound test has become ingrained in Federal Circuit case law as the exclusive test to be applied in all new chemical compound cases. As such, the test is widely used by district courts throughout the country, even by those courts that recognize that the statement made by the Federal Circuit in *Yamanouchi* was "not the creation of a new legal requirement, but merely a factually-specific application of the 'motivation-suggestion-teaching' test." *Janssen Pharmaceutica N.V. v. Mylan Pharms., Inc.*, 456 F. Supp. 2d 644, 657 n.4 (D.N.J. 2006).

*Second*, as the history of the lead compound test demonstrates, *Eli Lilly*, a pre-*KSR* case using the TSM test, and *Takeda*, a post-*KSR* case utilizing the TSM test, have played an important role in perpetuating a cramped view of *KSR*'s intention with respect to flexibility in an obviousness analysis. Both cases were submitted to this Court for review of whether the Federal Circuit had applied the TSM test in a manner inconsistent with the flexible approach advocated in *KSR*. And in both situations, certiorari was denied. *Eli Lilly*, 471 F.3d. 1369, cert. denied, *Teva Pharms. USA, Inc. v. Eli Lilly & Co.*, 552 U.S. 941 (2007); *Takeda*, 492 F.3d 1350, cert. denied, 552 U.S. 1295 (2008). Denial of certiorari in

*Eli Lilly* and *Takeda* bolsters the justification for granting certiorari in this case. That this case follows *Eli Lilly* and *Takeda* exemplifies how the lead compound test has evolved over the years into a standard that can never be met.[10]

*Third*, because the Federal Circuit has exclusive jurisdiction over patent appeals, unless this Court intervenes, the law of obviousness as applied to new chemical compounds will not change. Just as it has occurred since 1984, the Federal Circuit will continue to reject every obviousness challenge of a patent claiming a new chemical compound for the sole reason that the lead compound test is impracticable to meet. Although chemical compound cases may seem arcane and inaccessible, this is not a reason to deny certiorari. At its heart, the subject matter of new chemical compound claims involves medicine. Millions of individuals have chronic ailments that

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[10] Mylan asserted in the Federal Circuit that, post-*KSR*, it is legal error to apply the obviousness standard in an overly rigid manner. The court nonetheless refused to flexibly construe the lead compound analysis. Specifically, the court disregarded its own statement in *Altana Pharma AG v. Teva Pharmaceuticals. USA, Inc.*, 566 F.3d 989, 1008 (Fed. Cir. 2009), that a "restrictive view of the lead compound test would present a rigid test similar to the teaching-suggestion-motivation test that [this Court] explicitly rejected in *KSR*," and found that the lead compound analysis "still requires the challenger to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds." (App. 18a (emphasis added).) Such an express refusal by the Federal Circuit to follow *Altana* provides this Court with another reason to review this important legal standard.

cannot be cured but can be treated with proper medication. The purpose of the Hatch-Waxman Act is not served if they cannot access *affordable* medication because of an overly rigid legal test.

*Fourth*, an alternative to the lead compound test has already been advocated in case law, but the Federal Circuit has resisted it. In fields where those of ordinary skill routinely manage unpredictability, the obviousness analysis should focus less on "predictability" *per se* and more on whether the alleged invention was "obvious to try," another theme stressed by *KSR*.

In short, until this Court speaks, its guidance in *KSR* will be disregarded in this important area of medicinal chemistry. The lead compound test will continue to "stifle, rather than promote, the progress of useful arts." *Id.* at 427. Instead of waiting for yet another challenge on this same ground, the Court should take this case.

## CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

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