No. 18-817

IN THE
Supreme Court of the United States

HIKMA PHARMACEUTICALS USA INC., AND WEST-WARD PHARMACEUTICALS INTERNATIONAL LTD., N/K/A HIKMA PHARMACEUTICALS INTERNATIONAL LTD.,
Petitioners,
v.

VANDA PHARMACEUTICALS INC.,
Respondent.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF IN OPPOSITION

Nicholas Groombridge
Counsel of Record
Eric Alan Stone
Kira Alexis Davis
Josephine Young
Daniel J. Klein

PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP
1285 Avenue of the Americas
New York, NY 10019
(212) 373-3212
ngroombridge@paulweiss.com

Counsel for Respondent

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QUESTION PRESENTED

Hikma's Petition wrongly asserts that the Federal Circuit declared all method-of-treatment claims to be "automatically" patent-eligible under Section 101, and asks this Court to decide:

> Whether patents that claim a method of medically treating a patient automatically satisfy Section 101 of the Patent Act, even if they apply a natural law using only routine and conventional steps.

That Question is not presented by the decision below or any other decision.

PARTIES TO THE PROCEEDINGS

The caption identifies all parties. Petitioners are Hikma Pharmaceuticals USA Inc., and West-Ward Pharmaceuticals International Ltd., N/K/A Hikma Pharmaceuticals International Ltd. (together, "Hikma"). The Respondent is Vanda Pharmaceuticals Inc.

CORPORATE DISCLOSURE STATEMENT

Vanda is publicly traded on the NASDAQ (symbol: VNDA). No publicly traded entity owns more than 10% of Vanda's stock.

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I. INTRODUCTION

Hikma's Petition rests on the premise that the Federal Circuit "effectively overruled" *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012) by exempting all method-of-treatment claims from 35 U.S.C. § 101 scrutiny, declaring all such claims "automatically" patent eligible. Pet. at Question Presented.

That premise is wrong. The Federal Circuit did not announce a categorical rule of patent eligibility for method-of-treatment patents.

Instead, the Federal Circuit faithfully applied this Court's precedents, including *Mayo*, to just the '610 patent claims, and held that those claims are not "directed to" a law of nature itself, but to a patent-eligible "appl[ication]" of such laws. *Alice Corp. Pty. v. CLS Bank Int'l*, 573 U.S. 208, 217 (2014) (citing *Mayo*, 566 U.S. at 71, 75-79). In dissent, Chief Judge Prost differed only as to the outcome of this case, and did not suggest that the majority was creating a new categorical rule. When the Federal Circuit denied Hikma's petition for review en banc, no judge (including Chief Judge Prost) dissented from that denial or warned that the court was trenching on this Court's decisions. And the Federal Circuit has considered patent eligibility in sixteen cases since the panel decision below, and found claims to be ineligible in fifteen of them. There is no crisis of patent eligibility at the Federal Circuit requiring this Court's review.

Nor has the Patent Office run amok by declaring all methods of treatment eligible for patenting, as Hikma warns. On the contrary. After Hikma filed this Petition the Patent Office issued proposed patent-eligibility guidance that treats the decision below as just one of many Federal Circuit decisions implementing—not overruling—this Court's precedents. The public comment period for that guidance extends until March of 2019.

This case is therefore a poor vehicle to review Hikma's Question Presented, because the decision below does not present that question and because these issues are percolating appropriately in the lower courts and the Patent Office.

This case is also a poor candidate for review on its facts. The '610 patent is exactly the kind of innovation the patent laws are intended to promote. It covers methods of safely administering one drug, iloperidone, to treat schizophrenia by administering specific doses to specified patient populations. Schizophrenia is a devastating, incurable condition with few approved treatments. The approved drugs can have debilitating side effects, and psychiatrists must often try several before finding one that a patient can tolerate. Over time, a drug can cease to work for an individual patient, requiring a switch to a new one. Iloperidone was an important addition to their armamentarium, both as another effective antipsychotic and because it has a markedly lower risk of a side effect called akathisia, a sense of inner restlessness so profound that it can induce suicide.

The invention of the '610 patent allowed this much-needed medicine to come to market. During early clinical development, certain patients taking iloperidone developed a potentially fatal cardiac side effect. Novartis, which owned the rights to iloperidone at the time, terminated the development program. FDA approved iloperidone only after Vanda's scientists determined which patients face that cardiac risk, why they face that risk, and whether there was any dosage that would be both safe and effective for those patients.

In the Hatch-Waxman Act, Congress specifically contemplated that patents like the '610 patent that claim "the use of" a molecule would be infringed by the submission of an Abbreviated New Drug Application ("ANDA") seeking approval for a generic drug. 35 U.S.C. § 271(e)(2)(A). Generic drug companies may, of course, argue that those patents are obvious, or not novel, and that they lack the required written description of a patent. Hikma made those arguments, lost at trial, and abandoned those defenses on appeal. What remains is a case-specific argument that these specific patent claims were ineligible for patenting under Section 101. The Federal Circuit's rejection of that argument warrants no review in this Court.

The Petition should be denied.

STATEMENT OF THE CASE

A. Iloperidone and QTc Prolongation

Iloperidone very nearly did not come to market, and would not have done so without the invention claimed by the '610 patent.

When the pharmaceutical giant Novartis initially tried to develop iloperidone for schizophrenia, patients began to show a side effect known as "QTc prolongation."

The Q and T waves are parts of the cardiac rhythm—picture two peaks on an EKG—and the "QTc interval" is the time between them, corrected ("c") for the patient's heart rate. An elongated QTc interval can cause sudden death. When QTc prolongation is observed in a clinical trial, the pharmaceutical company usually abandons the drug in development.

That happened here. When iloperidone was shown to cause QTc prolongation in some patients and Novartis could not determine the cause or devise a means to mitigate it, Novartis abandoned its years of development efforts despite having already invested hundreds of millions of dollars. Novartis sold the rights to develop iloperidone to Vanda in 2004 for just $500,000.

B. Vanda's Invention and FDA Approval

Vanda's scientists set out to determine the causes of iloperidone-induced QTc prolongation,

hoping to develop a method for its safe administration that preserved its efficacy and would satisfy FDA.

Their efforts proved fruitful. They discovered that iloperidone and one of its metabolites, known as P88, inhibited an electric channel in the heart called the "hERG channel" that could cause prolongation of the QT interval, while another iloperidone metabolite, known as P95, did not. Importantly, and unrelated to their effects on the heart, iloperidone and P88 are active in the brain in treating schizophrenia while P95 is not. Vanda's scientists also discovered that patients who, because of a genetic mutation, produce a lower-than-normal amount of a liver enzyme known as CYP2D6 (so-called "CYP2D6 poor metabolizers") appeared to be more at risk of iloperidone-induced QTc prolongation than patients with normal CYP2D6 metabolic function.

Among other things, the CYP2D6 enzyme is responsible for breaking down both iloperidone and P88, and for producing P95. They also found a correlation between QTc prolongation and the ratio of P88 to P95 in the blood, and a correlation with the ratio of (P88+iloperidone) to P95. They concluded that a patient with decreased CYP2D6 metabolism will have a substantially higher ratio of P88 to P95 than would a normal metabolizer, and can therefore be treated with less iloperidone to achieve therapeutic efficacy. Separately, because both P88 and iloperidone create the risk of QTc prolongation, while P95 does not, a CYP2D6 poor

metabolizer would have an increased risk of iloperidone-induced QTc prolongation given the same iloperidone dosage that a normal CYP2D6 metabolizer would have.

By combining these several independent discoveries, Vanda's scientists were able to formulate a safe and effective treatment regimen: a specific dosage range at which a CYP2D6 poor metabolizer can be effectively treated with iloperidone without an increased risk of QTc prolongation.

These discoveries were a breakthrough, and Vanda succeeded where Novartis had tried and failed. The district court found that Vanda's successes paved the way to FDA approval: "Vanda was able to obtain FDA approval for iloperidone based, at least in part, on the invention disclosed in the '610 patent . . . ." App. 4a. Demonstrating the value of Vanda's work, Novartis paid Vanda $200 million to re-acquire the rights to iloperidone after FDA approval, or 400 times what Vanda had paid Novartis for those rights just five years earlier.

Importantly, the invention of the '610 patent is limited to iloperidone. Whether genetic variations in CYP2D6 efficacy will alter the safety profile or the efficacy of any other drug depends on many, drug-specific factors: the extent to which the drug is processed by CYP2D6, whether other metabolic pathways will compensate for poor CYP2D6 metabolism, and whether the resulting metabolites will have effects similar to, stronger than, or weaker than the original drug. 1 C.A. App. 7216-7217.

C. The District Court Proceedings

After FDA approved iloperidone for the treatment of schizophrenia, Hikma's predecessor filed an Abbreviated New Drug Application seeking FDA-approval to sell iloperidone. Vanda sued, asserting the '610 patent and the now-expired patent on the iloperidone molecule.

The district court presided over a five-day bench trial, after which it found the asserted claims of the '610 patent infringed, non-obvious, not invalid for lack of written description, and not invalid for lack of patent-eligible subject matter. App. 69a-90a.

As relevant here, the district court found that under Step One of this Court's Section 101 test, the claims of the '610 patent "depend upon laws of nature," but that under Step Two "the process of using . . . genetic test[s] to inform the dosage adjustment recited in the claims was not routine or conventional . . . ." App. 76a-78a.

Notably, Hikma presented law-of-nature arguments in the district court that it then abandoned. Initially, Hikma posited a supposed natural law that "where a patient poorly metabolizes a drug, the patient should receive less drug." 1 C.A. App. 7323-7324. Hikma abandoned that because it is wrong as a matter of science; for some drugs, poor metabolizers should receive higher doses, not lower doses. *Id.* at 7323. Then Hikma suggested that the natural law is that "the more iloperidone you have in your system the higher the side effects would be." *Id.* That, too, is wrong; some

iloperidone side-effects are not dose-dependent at all. *Id.* at 7323-7324.

D. The Federal Circuit Decision

At the Federal Circuit, Hikma posited yet another natural law: that "the asserted claims are directed to a natural relationship between iloperidone, CYP2D6 metabolism, and QT prolongation." C.A. Dkt. No. 24 at 47.

The Federal Circuit exhaustively examined this Court's patent-eligibility precedents. The majority opinion held that the '610 patent claims—unlike the diagnostic-method claims in *Mayo*—are not "directed to" a law of nature, but to a concrete method of treating specific patients with specific dosages:

> At bottom, the claims here are directed to a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome. They are different from *Mayo*. They recite more than the natural relationship between CYP2D6 metabolizer genotype and the risk of QTc prolongation.

App. 35a. "Thus, the '610 patent claims are 'a new way of using an existing drug' that is safer for patients because it reduces the risk of QTc prolongation." App. 32a.

Chief Judge Prost dissented, and would have held that these claims are ineligible for patenting.

Notably, the dissent did not suggest that the majority was creating any new categorical rule for method-of-treatment claims. Chief Judge Prost simply would have reached a different outcome *in this case*. And it was central to the dissent that the use of iloperidone to treat schizophrenia "long predated the '610 patent," as in *Mayo* where the thiopurine drugs were in use long before the Mayo patent. App. 47a-48a. Respectfully, the undisputed record evidence contradicted that premise: The priority date of the '610 patent is five years before FDA approved iloperidone, and thus physicians did not use iloperidone to treat schizophrenia "long" (or, at all) before the '610 patent.

Hikma sought en banc review. The Federal Circuit denied that request, without dissent. App. 93a-94a.

REASONS FOR DENYING THE PETITION

Hikma's petition rests on the false premise that the Federal Circuit held that all method-of-treatment patent claims are "automatically" eligible for patenting under Section 101, *see* Pet. at Question Presented, supposedly overruling this Court's Section 101 precedents.

The Federal Circuit did not exempt method-of-treatment claims from Section 101 scrutiny. Instead, as Vanda shows below in **Section I**, the Federal Circuit exhaustively reviewed this Court's Section 101 decisions and sought to apply them to the facts of only this case. It made no statements

announcing a broad exemption for all method-of-treatment patents.

And as Vanda shows below in **Section II**, the majority opinion was correct on the merits. The '610 patent claims are exactly the type of claims that are patent-eligible under Section 101. Unlike the claims in *Mayo*, these claims do not simply describe a natural relationship in the human body and tell doctors to consider whether a dosage adjustment is indicated. The '610 patent claims require doctors to give specific dosages of iloperidone to specific patient populations. That the inventors discovered the physiological processes that make the dosages safe and effective does not convert their patent into a monopolization of the underlying physiological processes themselves. The scientific discoveries disclosed in the patent are available to all.

Hikma's and its amici's fears of a sea change if the Federal Circuit's decision is not reversed are unfounded, as Vanda shows in **Section III**. Hikma warns that drug companies will now list more method-of-treatment patents in the FDA's Orange Book and thereby improperly obtain 30-month stays of FDA approval for generic drugs. But Congress specifically contemplated that method-of-use patents would be infringed by the submission of a generic's ANDA, *see* 35 U.S.C. § 271(e)(2)(A), drug companies are already *required* to list method-of-treatment patents in the Orange Book, and thousands of method-of-treatment patents are already listed.

Hikma's and its amici's purported concerns reveal what is really at stake here: The generic-drug industry wants this Court to hold that all method-of-treatment patents are ineligible under Section 101 because they depend on the body's physiological response to a foreign substance. That would defy this Court's recognition that a "new way of using an existing drug" could be patent-eligible. *Mayo*, 566 U.S. at 87. And it would defy Congress's intent to make submission of an ANDA an act of infringement of method-of-use patents.

Finally, Hikma's and its amici's stated concerns about the Patent Office are also misplaced, as Vanda shows in **Section IV**. The Patent Office memorandum on which Hikma relies says only that method-of-treatment claims that "***apply***" natural relationships, "as opposed to being 'directed to' them," are eligible for patenting. App. 98a (emphasis in original). Since Hikma filed its Petition, the Patent Office has promulgated new proposed Section 101 rules, and they say nothing about an exemption for all method-of-treatment claims. 2019 Revised Patent Subject Matter Eligibility Guidance, 84 Fed. Reg. 50 (Jan. 7, 2019).

In sum, everything is percolating in the lower courts as this Court instructed. Certiorari is not warranted.

I. THE FEDERAL CIRCUIT FAITHFULLY APPLIED—AND ANNOUNCED NO CATEGORICAL EXEMPTION FROM—THIS COURT'S SECTION 101 PRECEDENTS

This Court's Section 101 precedents distinguish between (i) patents that are "directed to" (that is, they seek to monopolize) laws of nature, which may not be eligible for patenting, and (ii) patents that simply apply laws of nature (which nearly all patents do), and which pose no eligibility concerns. The distinction between claims that seek to monopolize laws of nature and claims that apply such laws reverberates through the Court's late-twentieth-century Section 101 jurisprudence and supports the two-step test of *Alice* and *Mayo*. *See Alice*, 573 U.S. at 217; *Mayo* 566 U.S. at 75-79.

1. That method-of-treatment claims may be patented is clear from Section 101 itself. The Patent Act begins by declaring that claims to a "process"—that is, method claims—are patentable:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. § 101 (emphasis added). Among the patentable processes are uses of drugs for therapy; those patents are specifically called out for inclusion in patent litigation over both generic drugs and biosimilars. *See* 35 U.S.C. § 271(e)(2)(A), (e)(2)(C);

42 U.S.C. § 262(*l*)(3)(A). All of these provisions must be read in pari materia. *See Erlenbaugh v. U.S.*, 409 U.S. 239, 243-44 (1972).

To be sure, this Court has held that despite the facial breadth of Section 101, one cannot patent, and thus monopolize, naturally occurring phenomena, because they are not "new," *Bilski v. Kappos*, 561 U.S. 593, 602 (2010), and one cannot patent, and thus monopolize, fundamental laws of nature or abstract ideas, which are concepts that should be reserved for "the storehouse of knowledge of all men," *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948).

Courts must "tread carefully in construing this exclusionary principle," however, "lest it swallow all of patent law." *Alice*, 573 U.S. at 217. That is because, "[a]t some level, 'all inventions . . . embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.'" *Id.* (quoting *Mayo*, 566 U.S. at 71).

To take a classic example, while Samuel Morse could not patent, and thus monopolize, the innate power of electro-magnetism to send messages at a distance (which Hikma highlights, Pet. at 6), he could patent the telegraph machines that depended on that innate power (which Hikma omits). *See Dolbear v. Am. Bell Tel. Co.* (*The Telephone Cases*), 126 U.S. 1, 534 (1888); *O'Reilly v. Morse*, 56 U.S. (15 How.) 62 (1854).

2. The distinction between patents "directed to" laws of nature and patents that merely apply those

natural laws reverberated through the Court's late-twentieth-century Section 101 cases.

In *Parker v. Flook*, on which Hikma focuses, the patent was directed to a method for updating numerical "alarm limits" during petrochemical and oil-refining catalytic-conversion processes, but the "only novel feature of the method" was the "mathematical formula" itself. 437 U.S. 584, 585 (1978).[1] The patent did not "purport to contain any disclosure relating to the chemical processes at work, the monitoring of process variables, or the means of setting of an alarm or adjusting an alarm system." *Id.* at 586. And it did not "purport to explain how to select the appropriate margin of safety, the weighting factor, or any of the other variables." *Id.* The Court analogized the claims to a patent on applying the formula for "determining the circumference of a wheel" or on the Pythagorean theorem, with "a final step indicating that the formula, when solved, could be usefully applied to existing surveying techniques." *Id.* at 590, 595. Such a patent would be directed to, and monopolize, the law of nature itself.

On the other hand, the Court stressed that "it is equally clear that a process is not unpatentable simply because it contains a law of nature or a mathematical algorithm." 437 U.S. at 590 (emphasis added) (citing *Eibel Process Co. v. Minn. & Ont. Paper Co.*, 261 U.S. 45 (1923)). The claim in

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[1] Hikma chides the Federal Circuit for not citing *Flook*. Pet. at 19. Neither party relied on *Flook* in the lower courts, or cited it other than in passing.

Eibel Process was to "an improvement on a papermaking machine that made use of the law of gravity." *Flook*, 437 U.S. at 590 n.12. A claim that merely relies on the actions of, but does not attempt to monopolize, a law of nature is eligible for patenting; what is ineligible, the Court held, is a patent claim "directed essentially to" an ineligible concept. *Flook*, 437 U.S. at 595 (emphasis added). "Very simply, our holding today is that a claim for an improved method of calculation, even when tied to a specific end use, is unpatentable subject matter under § 101." *Id.* at 595 n.18 (emphasis added).

This Court's subsequent decision in *Diamond v. Diehr*, 450 U.S. 175 (1981), "established a limitation on the principles articulated in *Benson* and *Flook*." *Bilski*, 561 U.S. at 611. As in *Flook*, the claims in *Diehr* covered the computerized use of a well-known mathematical formula in a method of molding rubber under heat and pressure. 450 U.S. at 177-78. The Court reasoned that the patentee did not "seek to patent a mathematical formula" itself, but rather an industrial process for the molding of rubber products. *Id.* at 187. While the process "employ[ed] a well-known mathematical equation," the patent would not "pre-empt the use of that equation," but only prohibit others from using that equation "in conjunction with all of the other steps in [the] claimed process." *Id.* The Court found the claims patent-eligible.

3. The "opposite conclusions" reached in *Flook* and *Diehr*, *Mayo*, 566 U.S. at 80, are at the heart of the Court's modern Section 101 decisions. In *Alice*,

the Court explained that the essence of the claims in *Flook* was a monopolization of the mathematical formula itself when deployed on a computer, while "the claims in *Diehr* were patent eligible because they improved an existing technological process." 573 U.S. at 223. And in *Mayo* the Court explained that the patent was upheld in *Diehr* "because of the way the additional steps of the process integrated the equation into the process as a whole." 566 U.S. at 80.

Relying on *Flook* and *Diehr*, the Court's decisions in *Alice* and *Mayo* set out the modern, two-step test for determining patent eligibility.

At **Step One**, "we determine whether the claims at issue are directed to one of those patent-ineligible concepts." *Alice*, 573 U.S. at 217 (citing *Mayo*, 566 U.S. at 75-79) (emphasis added). If the claim is not directed to an ineligible concept, it is eligible for patenting.

If the claim is "directed to" an ineligible concept, at **Step Two** "we then ask, 'what else is there in the claims before us.'" *Alice*, 573 U.S. at 217. "To answer that question," a court considers the claim elements individually and as an ordered combination, to determine whether the elements beyond the claimed law of nature "'transform the nature of the claim' into a patent-eligible application" of that law of nature. *Id.* (quoting *Mayo*, 566 U.S. at 78). The Court has described this as a search for "an inventive concept." *Alice*, 573 U.S. at 217.

Hikma's Question Presented asserts that method-of-treatment claims that "apply" natural laws fail Step One, and that their patent eligibility must be determined at Step Two. *See* Pet. at Question Presented. Hikma misreads *Alice* and *Mayo*. If merely "apply[ing]" a natural law caused a claim to fail Step One, the "exclusionary principle" of those cases could "swallow all of patent law," *Alice*, 573 U.S. at 217 (citing *Mayo*, 566 U.S. at 71), and the *Alice*/*Mayo* test would collapse down into only Step Two. That is because, as the Court warned in *Alice* and *Mayo*, "[a]t some level, 'all inventions . . . apply laws of nature . . . .'" *Alice*, 573 U.S. at 217 (quoting *Mayo*, 566 U.S. at 71) (emphases added).

At Step One, then, a court may not merely determine whether the claim applies or relies on laws of nature—the answer to which would essentially always be "yes"—but must instead determine whether a patent claim is "directed to" a patent-ineligible concept. *Alice*, 573 U.S. at 217 (emphasis added).

The claims in *Alice* were directed to the abstract idea of an intermediated settlement, "a fundamental economic practice long prevalent in our system of commerce," *id.* at 219 (citation and internal quotation marks omitted), and sought to monopolize computerized implementation of that abstract idea. Further scrutiny at Step Two was therefore needed.

Likewise, in *Mayo*, the diagnostic claims were directed to laws of nature, specifying and purporting to monopolize "relationships between concentrations

of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." *Mayo*, 566 U.S. at 77. Critically, the claims did not require the doctor to perform any particular treatment; infringement occurred merely from the doctor's measuring the metabolites and considering the results. *Id.* at 86-87. A doctor would infringe Mayo's patent even if the "subsequent treatment decision" does not "change in light of the inference he has drawn using the correlations" described in the patent. *Id.* Step Two scrutiny was therefore required.

Nothing in those cases, however, suggests—as Hikma would have it—that Step Two scrutiny is required any time a claim applies a law of nature.

On the contrary, the Court noted that the *Mayo* diagnosis claims were unlike "a typical patent on a new drug or a new way of using an existing drug," which "confine their reach to particular applications of" natural laws. 566 U.S. at 87 (emphases added). And while the Court later invalidated as patent-ineligible claims to naturally occurring DNA sequences, the Court again noted that claims to natural phenomena themselves are different than "method claims" and claims on "*new applications* of knowledge about" the claimed DNA sequences. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 595-96 (2013) (italics in original).

4. The Federal Circuit faithfully applied this Court's Section 101 precedents.

Far from "effectively overrul[ing]" *Mayo*, as Hikma contends, *see* Pet. at 1, the Federal Circuit cited *Mayo* on every page of its Section 101 analysis and sought to apply *Mayo, Alice*, and *Myriad* to the facts of this case. And far from "exempt[ing]" method-of-treatment claims from the Section 101 analysis, *see* Pet. at Question Presented, the Federal Circuit limited its discussion to the '610 patent.

Vanda discusses the merits of that decision further in Section II below, but what matters here is that the Federal Circuit did not purport to announce a categorical rule for all method-of-treatment patents. Central to its resolution of this case was that the claims here "are directed to a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome." App. 35a. The court contrasted that specificity with "the claim at issue in *Mayo*," and concluded that, as foreshadowed by *Mayo*, "the '610 patent claims are 'a new way of using an existing drug' that is safer for patients because it reduces the risk of QTc prolongation." App. 32a (quoting *Mayo*, 566 U.S. at 87). And unlike the claims in *Mayo*, which this Court found were "directed to" a law of nature itself, the Federal Circuit found that the '610 patent does not "claim"—and thus seek to monopolize—"the relationships between iloperidone, CYP2D6 metabolism, and QTc prolongation," but rather claims only "an application of that relationship." App. 32a (emphasis added).

Chief Judge Prost's dissent, too, was about only the '610 patent. The dissent did not suggest that the majority was enacting a categorical rule, or overruling *Mayo*, or otherwise systematically flouting this Court's decisions. When the Federal Circuit denied Hikma's request for en banc review, no member of that court dissented from that denial or suggested that the *Vanda* decision effected a sub silentio overruling of this Court's cases.

The Federal Circuit's subsequent decisions confirm its fidelity to this Court's jurisprudence. The Federal Circuit has addressed Section 101 in sixteen decisions since the panel decision below, and it held patent claims to be ineligible in fifteen of them.[2] In the most recent such decision, the

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[2] *See Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, No. 2017-2508, 2019 WL 453489 (Fed. Cir. Feb. 6, 2019) (invalid claim to natural law; method of diagnosing a neurological disorder); *In re Marco Guldenaar Holding B.V.*, 911 F.3d 1157 (Fed. Cir. 2018) (invalid claim to abstract idea; rules for playing games); *Data Engine Techs. v. Google LLC*, 906 F.3d 999 (Fed. Cir. 2018) (invalid claim to abstract idea; methods of tracking data changes in a spreadsheet); *Roche Molecular Sys., Inc. v. Cepheid,* 905 F.3d 1363 (Fed. Cir. 2018) (invalid claim to natural phenomenon; method for detecting pathogenic bacterium); *BSG Tech LLC v. BuySeasons, Inc.*, 899 F.3d 1281 (Fed. Cir. 2018) (invalid claim to abstract idea; methods for indexing information); *SAP Am., Inc. v. InvestPic, LLC*, 898 F.3d 1161 (Fed. Cir. 2018) (invalid claim to abstract idea; methods of calculating, analyzing, and displaying investment data); *Interval Licensing LLC v. AOL, Inc.*, 896 F.3d 1335 (Fed. Cir. 2018) (invalid claim to abstract idea; non-overlapping onscreen presentation of two sets of information); *Praxair Distrib., Inc. v. Mallinckrodt Hosp. Prods. IP Ltd.*, 890 F.3d 1024 (Fed. Cir. 2018) (invalid claim to printed matter; method for providing prescribing information relating to a

Federal Circuit described the *Vanda* decision not as a categorical watershed for method-of-treatment claims, but simply as a decision about the facts of this case: "holding that method of treatment by administering drug at certain dosage ranges based on a patient's genotype was not directed to a natural law." *Athena*, 2019 WL 453489, at *6.[3]

Far from unleashing a flood of pro-patentee Section 101 decisions, the *Vanda* decision is just one case in a pattern of decisions faithfully applying this Court's *Alice/Mayo* precedent.

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harmful side effect); *Voter Verified, Inc. v. Election Sys. & Software LLC*, 887 F.3d 1376 (Fed. Cir. 2018) (invalid claim to abstract idea; methods for self-verifying); *see also Glasswall Sols. Ltd. v. Clearswift Ltd.*, No. 2018-1407, 2018 WL 6720014 (Fed. Cir. Dec. 20, 2018) (invalid claim to abstract idea; filtering of electronic files and data); *In re Downing*, No. 2018-1795, 2018 WL 6436437 (Fed. Cir. Dec. 7, 2018) (invalid claim to abstract idea; creating an electronic spreadsheet for personal management); *In re Villena*, 745 F. App'x 374 (Fed. Cir. 2018) (invalid claim to abstract idea; property valuation); *Burnett v. Panasonic Corp.*, 741 F. App'x 777 (Fed. Cir. 2018) (invalid claim to abstract idea; converting geospatial coordinates into natural numbers); *In re Wang*, 737 F. App'x 534 (Fed. Cir. 2018) (invalid claim to abstract idea; phonetic symbol system); *In re Eberra*, 730 F. App'x 916 (Fed. Cir. 2018) (invalid claim to abstract idea; product promotion).

[3] The *Athena* case shows that Section 101 issues are percolating in the academy as well as the lower courts. Hikma's *amici* include law professors. But in *Athena*, ten other law professors urged that the claims were patent-eligible. Brief of Amici Curiae Ten Law Professors (Nov. 13, 2017), ECF No. 54.

II. THE '610 PATENT CLAIMS ARE PATENT-ELIGIBLE UNDER THIS COURT'S PRECEDENT

A writ of certiorari is rarely appropriate to correct "erroneous factual findings or the misapplication of a properly stated rule of law" (Sup. Ct. Rule 10), but here the writ is even less appropriate because the Federal Circuit made no erroneous finding of fact or conclusion of law. On the contrary, the claims of the '610 patent are exactly the type of innovation that the Patent Act encourages and rewards.

1. The '610 patent inventors' work paved the way for FDA to approve iloperidone. Thus, while Hikma characterizes the '610 patent claims as "the administration of a known drug for a known use," Pet. 20, 37; *accord* Amicus Br. of The Association for Accessible Medicines, et al. ("Inventia Br.") at 14-15 & n.14), the undisputed evidence belies that characterization.

Iloperidone was not approved for use at all before the invention of the '610 patent. Instead, iloperidone's tendency to induce QTc prolongation stalled its commercial development. Novartis—the world's fourth largest pharmaceutical company by annual revenue ($52.54 billion in 2017)—could not solve the QTc problem. It abandoned iloperidone and sold the rights to the pharmaceutical compound to Vanda for $500,000. Through the invention of the '610 patent, Vanda satisfied FDA that iloperidone could safely treat CYP2D6 poor metabolizers. Novartis then repurchased the rights from Vanda,

at a price 400 times higher than what Vanda paid Novartis just a few years earlier.

The district court found that Vanda obtained FDA approval for iloperidone "at least in part" because of the '610 patent's claimed method of reducing "the side effects associated with QTc prolongation in order to safely treat patients suffering from schizophrenia." App. 72a-73a. Hikma did not challenge that finding on appeal. [4]

2. The '610 patent inventors' scientific analysis and inventive application of their findings is exactly the type of work that the patent laws should protect. They studied genetics, liver metabolism, cardiac electrical channels, and brain activity to find a safe way to treat specific psychiatric conditions with a specific compound at specified doses. They then patented only the specific method of treatment they developed, not the underlying natural processes.

When the inventors began their work, much was unknown. No one knew why iloperidone was

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[4] Inventia—which purports to be a friend of the Court but has also been sued by Vanda under this very patent—asserts that the appropriate iloperidone dose for a CYP2D6 poor metabolizer was in the prior art, relying on the Jain reference. (Inventia Br. at 14-15 & n.14). That is incorrect. In allowing the '610 patent claims, the Patent Office noted that none of the prior art, including Jain, taught or suggested adjusting the dosage "based on a determination of the presence or absence of a CYP2D6 poor metabolizer genotype." 1 C.A. App. 2877. Indeed, Jain completely missed that some patients taking 24 mg/day of iloperidone were at risk of serious cardiac complications. The '610 inventors solved a problem that Jain overlooked.

associated with QTc prolongation. For example, some people are genetically predisposed to have elongated QTc intervals, and the QTc prolongation seen when administering iloperidone might have had nothing to do with iloperidone at all. Or the QTc prolongation could have had something to do with the body's metabolism of iloperidone, and been caused by iloperidone itself, or one or some of its many metabolites.

By studying iloperidone metabolism and data about genetic mutations seen in some patients taking iloperidone, the '610 patent inventors determined that QTc prolongation was more prevalent in CYP2D6 poor metabolizers given iloperidone.

The district court found that at the time of the '610 patent invention, it was not known how the CYP2D6 enzyme metabolized iloperidone, or the effects on the body of the resulting metabolites. Rather, it was known that some CYP2D6-metabolized drugs should be given in higher doses to CYP2D6 poor metabolizers, while others should be given in lower doses, while still others should not be given to CYP2D6 poor metabolizers at all. App. 72a.

The '610 patent inventors learned that iloperidone itself and a metabolite of iloperidone called P88 each have anti-schizophrenic effects in the brain and each also inhibit the heart's hERG channel, which can result in elongated QTc intervals. They also learned that the enzyme CYP2D6 plays two roles in the metabolism of

iloperidone: it results in a metabolite called P95, which is not active in the brain and which also does not inhibit the hERG channel in the heart, and it breaks down the other significant metabolite, P88.

The inventors then realized that both anti-schizophrenic efficacy and the risk of QTc prolongation depend on the ratio in the patient's blood of iloperidone to P95, and on the ratio of (iloperidone+P88) to P95. A person with diminished CYP2D6 functionality (i) needs less iloperidone to achieve anti-schizophrenic efficacy, and (ii) is at an increased risk of iloperidone-induced QTc prolongation, because she has more iloperidone and P88 and less P95 in her blood than a patient with normal CYP2D6 functionality. Using this knowledge, the inventors determined that CYP2D6 poor metabolizers could be treated both safely and efficaciously with a dose of 12 mg/day or less of iloperidone, where normal metabolizers could be safely and efficaciously treated with a dose of more than 12 mg/day and up to 24 mg/day.

3. Hikma contends that this was all just the discovery of a "natural law," namely that "a risk of QTc prolongation for a patient having a CYP2D6 poor metabolizer genotype is lower following the internal administration of 12 mg/day or less." Pet. at 11-12.

If the manner in which a specific drug is metabolized by a specific enzyme is a "natural law," then the invention of the '610 patent is a practical application of not one natural law but of at least

seven such laws, spanning four discrete parts of the body:

In the Brain

- Iloperidone and P88 bind to neurological receptors, giving iloperidone its efficacy as a schizophrenia treatment.

- P95 does not bind to those neurological receptors.

In the Heart

- Iloperidone and P88 inhibit the cardiac hERG channel, creating a QTc prolongation risk.

- P95 does not inhibit the hERG channel.

In the Liver

- Metabolism of iloperidone through the CYP2D6 enzyme results in P95.

- CYP2D6 degrades P88.

In the Patient's Genome

- Some people have genetic mutations that result in decreased CYP2D6 functionality.

What is notable about these "natural laws" is that the '610 patent does not claim any of them, as the Federal Circuit found. "The inventors recognized the relationships between iloperidone, CYP2D6 metabolism, and QTc prolongation, but

that is not what they claimed. They claimed an application of that relationship." App. 32a (emphases added).

And the specification of the '610 patent recites every one of these scientific discoveries about iloperidone metabolism, safety, and efficacy.[5] By disclosing those scientific discoveries but not claiming them, the '610 patent inventors dedicated those discoveries to the public. *See, e.g.*, *Miller v. Bridgeport Brass Co.*, 104 U.S. 350, 352 (1881).

For example, scientists or doctors or lawyers can use the knowledge that P88 inhibits the hERG channel however they wish. They can use the knowledge that CYP2D6 degrades P88. They can investigate whether similar metabolic pathways and genetic mutations combine to create a risk of QTc prolongation for a compound other than iloperidone. They can even develop a method of dosing iloperidone itself to reduce the risk of QTc

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[5] The '610 patent specification discloses that iloperidone is active in the brain to treat schizophrenia and that P88 has a similar "pharmacological profile," *see* 1 C.A. App. 38, 44 ('610 patent, col. 1, ll. 34-47; col. 13, ll. 15-22); that P95 is viewed as "pharmacologically inactive," *see id.* at 39 ('610 patent, col. 4, ll. 49-53); that iloperidone and P88 activate the hERG channel, *see id.* ('610 patent, col. 4, ll. 37-53); that P95 does not activate the hERG channel, *id.*; that CYP2D6-induced metabolism of iloperidone results in P95; that CYP2D6 degrades P88, *see id.* at 40 ('610 patent, col. 6, ll. 57-59); and that a person's genetic profile can dictate her CYP2D6 enzymatic functionality, including the relative concentrations of P88 and P95 in patients given iloperidone, *see id.* at 40-41 ('610 patent, col. 6, l. 54 to col. 8, l. 31).

prolongation that is different than the methods claimed by the '610 patent.

The '610 patent claims only a specific application of its inventors' work: treating a patient with schizophrenia using iloperidone by determining, through a genotyping test, whether the patient is genetically predisposed to CYP2D6 poor metabolism and then administering one of two specified doses of iloperidone depending on the results of that test.

Contrary to Hikma's argument, *Flook* does not mean that these treatment elements are mere "post-solution activity." In fact, *Flook* provides a useful contrast. In explaining what kind of claim would add insignificant post-solution activity to an ineligible concept, *Flook* stated that "the Pythagorean theorem would not have been patentable, or partially patentable, because a patent application contained a final step indicating that the formula, when solved, could be usefully applied to existing surveying techniques." 437 U.S. at 590; *see also Diehr*, 450 U.S. at 191-92 (explaining *Flook*'s holding as rendering "insignificant post-solution activity" impermissible (emphasis added)); *accord Bilski*, 561 U.S. at 610-11. By comparison, the concrete elements of the '610 patent claims requiring the administration of specific dosages of iloperidone to specific subpopulations of patients was part of, and necessary to, accomplishing the solution provided by the claims: the relative risk reduction of iloperidone-induced QTc prolongation. The treatment elements are neither "insignificant" nor "post-solution." They are critical to the utility of

the claimed method and intertwined throughout the method of treatment itself.

4. The '610 patent claims are therefore like the claims in *Diehr* and *Eibel Process*: "an application of a law of nature or mathematical formula" to a previously unknown and unavailable treatment and thus "deserving of patent protection." *Diehr*, 450 U.S. at 187 (emphasis in original). Unlike in *Flook*, the '610 patent claims are not "directed essentially to" a law of nature. *Flook*, 437 U.S. at 595. The claims pose no risk of "tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries," *Mayo*, 566 U.S. at 73, but foreclose others from their use only "in conjunction with all of the other steps of the[] claimed process[es]," *Diehr*, 450 U.S. at 187. Their "substantial practical application" is not for carrying out any particular law of nature, *Gottschalk v. Benson*, 409 U.S. 63, 71-72 (1972), but to a "new way of using an existing drug," *Mayo*, 566 U.S. at 87, one that allowed the drug to be legally prescribed in the United States.

Hikma's Petition demonstrates this graphically. In its chart, Pet. at 34-35, Hikma compares the elements of the *Mayo* claims to claim 1 of the '610 patent. Notably, even Hikma finds no analogue in the *Mayo* patent to the dosage step in the '610 patent. *See* Pet. at 35. That is exactly right. The diagnostic method in *Mayo* did not require the doctor to do anything based on the observed metabolite levels, and the Mayo inventors did not invent or determine an appropriate dosage for a

drug or any other treatment step based on the diagnostic inquiry. What they sought to patent, this Court held, was the natural relationship among the metabolites itself. Hikma makes much of the fact that the *Mayo* claims "covered the administration of a specific drug (thiopurine)," Pet. at 8, but that administration was simply a prerequisite to being able to claim the observation of the relationship of the thiopurine metabolites. *Mayo*, 566 U.S. at 77 ("While it takes a human action (the administration of a thiopurine drug) to trigger a manifestation of this relation in a particular person, the relation itself exists in principle apart from any human action."). In deciding that this case "is not *Mayo*" App. 31a, and that the claims here are not "directed to" a law of nature at Step One of the *Alice/Mayo* test, the Federal Circuit committed no error.

5. Finally, much of Hikma's Petition argues that the steps of the '610 patent are "routine and conventional" uses of a law of nature. That is the Step Two inquiry of the *Alice/Mayo* framework, and therefore has no bearing on the Question Presented, which addresses only whether the Federal Circuit has deemed that method-of-treatment claims are categorically patent-eligible at Step One.

Even accepting the premise that the '610 patent is "directed to" a law of nature at Step One, however, its claim elements are not routine and conventional at Step Two. Hikma seizes on statements in Chief Judge Prost's dissent to argue that "[t]he audience of physicians treating schizophrenia with iloperidone long predated the

'610 patent." Pet. at 20 (quoting App. 48a (Prost, C.J., dissenting)); *see also* Pet. at 18 (quoting App. 44a (Prost, C.J., dissenting)). As set forth above, the record belies this. Iloperidone use was not routine or conventional before the '610 patent. It was illegal; FDA had not yet approved iloperidone.

Hikma also contends that the administration elements are "routine and conventional" because it would be routine to perform studies to ascertain the correct iloperidone dosages for specific patient subpopulations. Pet. at 37. That answers the wrong question. Step Two asks whether the additional elements of the patent claim are routine and conventional, *Mayo*, 566 U.S. at 82; *Alice*, 573 at 221-22, not whether the inventors used routine and conventional means to make their invention. Moreover, it gets the answer wrong. Hikma's expert conceded at trial that clinical-trial design is not routine or conventional, the district court found that the '610 inventors' work was not obvious, and Hikma chose not to appeal that finding. If their work was non-obvious, it cannot have been "well-known in the art," which is the hallmark of the routine-and-conventional inquiry at Step Two. *See, e.g.*, *Mayo*, 566 U.S. at 79.

III. THE DECISION BELOW WILL NOT DELAY ACCESS TO GENERIC DRUGS OR HARM SOCIETY

The natural-law, abstract-idea, and natural-phenomena exceptions to patentability exist to protect innovation: monopolization of those basic tools of scientific research "might tend to impede

innovation more than it would tend to promote it." *Mayo*, 566 U.S. at 71. In *Mayo*, the American Medical Association and other leading physician groups as *amici* warned of the risks of monopolizing "'the body's natural responses to illness and medical treatment.'" *Id.* at 91 (quoting physician amicus brief). Likewise, the challenge to the patents in *Myriad* was brought by, among others, "medical patients, advocacy groups, and . . . doctors." 569 U.S. at 586.

Notably, Hikma has no *amicus* support from doctors, from patients, or from innovators of any kind. Its support comes from academics, professional lobbyists, and other generic-drug companies.

Protecting their own interests, they warn that the decision will incentivize innovators to list patent-ineligible method-of-treatment patents in the FDA "Orange Book" and improperly obtain 30-month-stays of FDA approval for a generic drug. But Congress explicitly contemplated that method-of-treatment patents would issue, and required innovators to list those patents in the Orange Book. And in the same Patent Act that includes Section 101, Congress provided that submitting an Abbreviated New Drug Application for a generic drug infringes not only patents on the drug itself, but patents on "the use" of that drug. 35 U.S.C. § 271(e)(2)(A) (emphasis added); *see Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 405 (2012). New Drug Application owners must list in the Orange Book "any patent which claims the drug

for which the applicant submitted the application or which claims a method of using such a drug . . . ." 21 U.S.C. § 355(b)(1) (emphasis added). The biosimilars statute likewise contemplates litigation over method-of-use patents. *See* 35 U.S.C. § 271(e)(2)(C); 42 U.S.C. § 262(*l*)(3)(A).

Hikma's and its amici's position, on the other hand, would radically rework the law of generic drugs (a result that Inventia's generic-drug-industry brief eagerly embraces). If a method-of-treatment patent is "directed to" a law of nature simply because its therapeutic efficacy depends on metabolic processes within the body (or, in Inventia's articulation, because "a patient's body determines if infringement occurs," Inventia Br. at 16), then an enormous number of patents specifically identified by the Patent Act will become ineligible for patenting.

Whether iloperidone treats schizophrenia at all depends on what happens in "a patient's body," yet no one contends that using iloperidone to treat schizophrenia would be unpatentable. Indeed, all methods of treatment depend, at some level, on what happens in a patient's body. Hikma begrudgingly concedes that Section 101 would permit a patent on the use of a known antiviral drug to treat cancer, *see* Pet. at 21-22, but never explains how that patent differs analytically from a patent on treating some schizophrenia patients with iloperidone at one dose and other patients at another dose.

Petitioner's amici go further, proposing a regime under which essentially all method-of-treatment patents would be ineligible. In their view, if an inventor were to discover that the standard dose of Tylenol effectively treats pancreatic cancer, the courts would deem that insight to be in the prior art and then ask only whether the dosage schedule was routine and conventional. *See* Inventia Br. at 12-14, 19; Amicus Br. of Intellectual Property and Innovation Professors, et al. at 7. There is no support for that position in this Court's cases, and it is irreconcilable with Congress's decision to make method-of-use patents part of generic-drug and biosimilar litigation.

IV. THE PATENT OFFICE HAS NOT CREATED A CATEGORICAL EXCEPTION FOR METHODS-OF-TREATMENT TO THIS COURT'S PRECEDENTS

Hikma suggests that the Patent Office reads the *Vanda* decision as "ensur[ing] that all future method-of-treatment patents will issue without undergoing any real scrutiny" at Step One of the *Alice/Mayo* analysis. Pet. at 29.

Hikma misreads the Patent Office guidance. That is clear both from the June 2018 Memorandum on which Hikma relies and from Subject Matter Eligibility Guidance that the Patent Office issued for public comment after Hikma filed its Petition.

The June 2018 Memorandum did not announce that all method-of-treatment claims are patent-eligible. Had that been the Patent Office's

conclusion, the Memorandum would have been one sentence long. Instead, the Memorandum stressed what this Court stressed in *Alice* and *Mayo* and the Federal Circuit repeated in the decision below:

- In assessing patent eligibility, claims must be evaluated "as a whole." App. 97a.

- Method-of-treatment claims that "***apply***" natural relationships, "as opposed to being 'directed to' them," are eligible for patenting. *Id.* at 98a (emphasis in original).

- Whether the other claim elements are "routine and conventional" is relevant at Step Two of the *Alice/Mayo* analysis (which the Patent Office calls Step 2B), but is not relevant if, at Step One (or, in the Patent Office parlance, Step 2A), the claim is not directed to a law of nature. *Id.*

From these principles, the June 2018 Memorandum concluded only what *Mayo* and *Alice* already taught: method-of-treatment claims should be considered patent-eligible at Step One of the *Alice/Mayo* test where those claims "practically apply," without being directed to, "natural relationships." *Id.* at 98a-99a.

The June 2018 Memorandum ended with the possibility of "further guidance in the area of subject matter eligibility in the future." *Id.* at 99a. The Patent Office released that Guidance on January 7, 2019. The new Guidance, too, differentiates "claims to principles in the abstract" and "claims that integrate those principles into a practical

application." 2019 Revised Patent Subject Matter Eligibility Guidance, 84 Fed. Reg. 50, 51 (Jan. 7, 2019). It proposes that "A claim is not 'directed to' a judicial exception, and thus is patent eligible, if the claim as a whole integrates the recited judicial exception into a practical application of that exception." *Id.* at 53. "A claim that integrates a judicial exception into a practical application will apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception, such that the claim is more than a drafting effort designed to monopolize the judicial exception." *Id.* (emphases added).

The Guidance is completely consistent with the law as this Court articulated it in *Mayo* and *Alice*. And it treats the decision below as a fact-specific application of this Court's precedents, not as a categorical exemption of method-of-treatment claims from those precedents. The Guidance describes the decision below as "holding claims to the practical application of the natural relationships between iloperidone, CYP2D6 metabolism, and QTc prolongation to treat schizophrenia, not merely the recognition of those relationships, to be patent eligible at *Mayo*/*Alice* step 1." *Id.* at 55 n.26.

Finally, the new Guidance confirms why this case is a poor vehicle for the Court to address Section 101 further. The Guidance notes that the law on Section 101 is "rapidly evolving," *id.* at 51, and it calls for public comment on the proposed Guidance by March 8, 2019. The Guidance itself

may evolve or change in response to public commentary. *Id.* at 57.

CONCLUSION

For the foregoing reasons, Hikma's Petition should be denied.

Respectfully submitted,

Nicholas Groombridge
Counsel of Record
Eric Alan Stone
Kira Alexis Davis
Josephine Young
Daniel J. Klein

PAUL, WEISS, RIFKIND,
WHARTON & GARRISON LLP
1285 Avenue of the Americas
New York, NY 10019
(212) 373-3212
ngroombridge@paulweiss.com

Counsel for Respondent

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