ORAL ARGUMENT NOT YET SCHEDULED
Nos. 15-5021 and 15-5022 (consolidated)

In the United States Court of Appeals for the District of Columbia Circuit

TAKEDA PHARMACEUTICALS U.S.A., INC., ET AL., APPELLANTS

v.

SYLVIA MATTHEWS BURWELL, ET AL., APPELLEES
HIKMA PHARMACEUTICALS PLC ET AL., INTERVENOR-APPELLEES

ON APPEAL FROM THE U.S. DISTRICT COURT FOR THE DISTRICT OF COLUMBIA NO. 14-01668, HON. KETANJI BROWN JACKSON, DISTRICT JUDGE

BRIEF FOR INTERVENOR-APPELLEES HIKMA PHARMACEUTICALS PLC AND WEST-WARD PHARMACEUTICALS CORP.

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CERTIFICATE OF PARTIES, RULINGS UNDER REVIEW, AND RELATED CASES

Pursuant to Federal Rule of Appellate Procedure 26.1 and Circuit Rules 26.1 and 28(a)(1), Hikma Pharmaceuticals PLC and West-Ward Pharmaceuticals Corp. (together, "Hikma") certify as follows:

A. Parties, Intervenors, and *Amici*

1. Takeda Pharmaceuticals U.S.A. ("Takeda") along with Elliott Associates, L.P., Elliott International, L.P., and Knollwood Investments, L.P. (collectively, "Elliott") are the Appellants in this case. They were plaintiffs in the underlying consolidated actions before the United States District Court for the District of Columbia to set aside agency action by the Food and Drug Administration ("FDA").

2. Sylvia Mathews Burwell and Margaret Hamburg, M.D., in their official capacities as Secretary, United States Department of Health and Human Services, and Commissioner of Food and Drugs, FDA, are Appellees in this case and were the defendants in the underlying actions.

3. Appellees and were the intervenor-defendants in the underlying actions.

4. Pharmaceutical Research and Manufacturers of America filed an amicus brief in support of appellants.

B. Ruling Under Review

Appellants seek review of the Summary Judgment Order and Memorandum Opinion entered on January 9, 2015, and January 12, 2015, by United States District Judge Ketanji Brown Jackson in the United States District Court for the District of Columbia, in Case No. 1:14-cv-01668-KBJ (District Court Dkt. # 68 & 74) and Case No. 1:14-cv-01850-KBJ (District Court Dkt. # 16).

C. Related Cases

The ruling under review was not previously before this Court or any other. Takeda filed an induced patent infringement lawsuit against Hikma Pharmaceuticals PLC and West-Ward Pharmaceutical Corp. (and also against Hikma Americas Inc.) in the United States District Court for the District of Delaware, Case No. 1:14-cv-01268-SLR. The district court granted a temporary restraining order, denied Takeda's motion for preliminary injunction, but maintained a temporary injunction pending appeal (Dkt. # 78 & 79). On January 9, 2015, the day of oral argument after expedited briefing, the United States Court of Ap-

peals for the Federal Circuit summarily affirmed the denial of the preliminary injunction and lifted the temporary injunction in Case No. 15-1139 (Dkt. # 72), noting that an opinion will follow. On May 6, 2015, the Federal Circuit issued its published opinion in the case. *Takeda Pharms. U.S.A. Inc. v. West-Ward Pharma. Corp.*, 785 F.3d 625, 630 (Fed. Cir. 2015), *reh'g denied*, Case No. 15-1139, Dkt. 87 (Aug. 19, 2015).

Respectfully Submitted,

/s/ Charles B. Klein

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CORPORATE DISCLOSURE STATEMENT

Pursuant to Federal Rule of Appellate Procedure 26.1, Intervenor-Appellees Hikma Pharmaceuticals PLC and West-Ward Pharmaceuticals Corp.certify as follows:

West-Ward Pharmaceutical Corporation is a wholly owned subsidiary of Eurohealth (U.S.A.) Inc., which is an indirect wholly owned subsidiary of Hikma Pharmaceuticals PLC, a publicly held corporation. Hikma Pharmaceuticals PLC has no parent corporation.

Respectfully Submitted,

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GLOSSARY

ANDA: Abbreviated New Drug Application

APA: Administrative Procedure Act

CYP3A4: Cytochrome P450 3A4

DDI: Drug-Drug Interaction

FDA: Food and Drug Administration

FDCA: Food, Drug, and Cosmetics Act

NDA: New Drug Application

P-gp: P-glycoprotein

INTRODUCTION

This case arises out of Appellants' attempt to rescind FDA approval for Hikma's colchicine drug product called Mitigare®. Dating back to the Byzantine Empire, colchicine has been used to treat a form of arthritis called gout. JA474. As FDA has explained, "colchicine is a well-known drug and the efficacy and safety of colchicine in gout is well accepted." JA 780. In fact, Hikma itself safely sold generic colchicine for decades before FDA began regulating it. But Hikma and other manufacturers had to stop marketing their generics after Takeda became the first company to obtain FDA approval for a single-ingredient colchicine product called Colcrys®. Armed with a new monopoly, Takeda hiked the colchicine price from "~10 cents/pill to $5/pill, creating new financial hardships for [gout] patients." JA965-66.

Relief was in sight when, in September 2014, FDA approved Hikma's application to re-launch its competing colchicine product. In January 2015—after the Federal Circuit rejected Takeda's separately-litigated patent claims and lifted a temporary injunction—Hikma launched Mitigare® along with an authorized generic, thus offering patients a lower-cost alternative.

This Court should reject Appellants' extraordinary request to pull Hikma's version of this ancient drug from the market. As shown below, the district court properly rejected Appellants' arguments in a well-reasoned, 77-page published decision.

First, Appellants primarily ask this Court to rescind Hikma's application to allow Takeda "to litigate any patent claims promptly, *before* FDA approves" the product. Takeda Br. 6. But Hikma did not invoke the Hatch-Waxman provision that triggers this pre-approval, patent-resolution process. As Takeda puts it, "[w]hen a 505(b)(2) applicant," such as Hikma, "relies on" a previously approved drug to obtain FDA approval, "the applicant must include 'certifications' to the patents listed" for that drug—thus potentially leading to pre-launch litigation. Takeda Br. 5. But Hikma's 505(b)(2) application did *not* rely on Takeda's drug (Colcrys®), or any of Takeda's data. Indeed, it is undisputed that Hikma's application "omitted any citation to Colcyrs." Takeda Br. 17. Thus, under the "quid pro quo" process established by Hatch-Waxman, Hikma owes no *quid* (a patent certification) for Takeda's *quo* (the Colcrys® data).

For its part, Elliott advances an argument eschewed by Takeda—namely, that Hatch-Waxman does not even require such a *quid pro quo*. But as the district court recognized, "Elliott's reading is a distortion of the statutory text, rather than a statement of its unambiguous plain meaning." JA84. The relevant regulations are to the same effect.

Aware of this difficulty, Takeda argues that even though *Hikma* did not rely on any Colcrys® data, *FDA* did—noting that the administrative record references Colcrys® "246 times." Takeda Br. 14. But these references simply confirm that FDA diligently studied whether Hikma needed to rely on the Colcrys® data and, after thorough analysis, properly concluded that Hikma did not need to do so. As the district court held, "Takeda has fallen short of making a persuasive argument that FDA's actions here—including its repeated 'substantive references to Colcrys data' … qualify as the type of reliance that Congress intended to give rise to the patent certification obligation." JA66.

Appellants' arguments are not only meritless, but pointless. Again, Appellants say they need time to address whether their patent rights can enjoin Hikma's product launch. But the Federal Circuit has already held that Takeda's patents cannot support such injunctive re-

lief—finding, for example, that the Mitigare® label is "not sufficient to establish induced infringement." *Takeda Pharms.*, 785 F.3d at 630. Appellants need no time, much less the 30 months they request, to re-litigate their failed claim for injunctive relief.

Second, Takeda alternatively asks the Court to rescind FDA approval on the ground that FDA failed to explain, in light of a prior citizen petition ruling, how the Mitigare® label safely omits the specific dose adjustments referenced in the Colcrys® labeling. But as the district court explained, this argument is "puzzling" given "the agency's clear and convincing record statements about why it permitted the Mitigare label to differ from that of Colcrys." JA91. Appellants' efforts to second-guess FDA's approval are particularly misplaced given the high level of deference accorded to agencies' safety-related scientific determinations. Indeed, when reviewing a "scientific determination," such as the safety of a drug, this Court "must generally be at its most deferential." *Baltimore Gas & Elec. Co. v. Natural Res. Def. Council, Inc.*, 462 U.S. 87, 103 (1983).

In sum, there is no basis to grant the extraordinary relief requested by Takeda and Elliott—to our knowledge, this Court has never re-

scinded FDA approval for a pharmaceutical product and required the product to be withdrawn from the market. The district court's ruling denying Appellants' summary judgment motions should be affirmed.

STATEMENT OF ISSUES

1. Did FDA arbitrarily and capriciously approve Hikma's new drug application for Mitigare® without requiring certifications to Takeda's patents when that application did not reference any Takeda product or data (JA775, 833-34)?

2. Did FDA arbitrarily and capriciously apply a prior citizen petition ruling when FDA, after expressly "consider[ing]" that ruling in light of Hikma's independent testing, the agency concluded "it was reasonable to forego [*sic*] detailed dose modification recommendations" (JA899); and when FDA further concluded, based on the limited indication for Mitigare®, that "it would be appropriate for the label to note that Mitigare should not be used" to treat acute gout flares (JA773)?

PERTINENT STATUTES

All applicable statutes and regulations are contained in the briefs for the Elliott and Takeda appellants.

REGULATORY BACKGROUND

The Hatch-Waxman Act requires drug manufacturers to seek FDA approval for new drugs through one of three pathways: (1) a full New Drug Application ("NDA"); (2) an Abbreviated New Drug Application ("ANDA"); or (3) an intermediate process known as a Section 505(b)(2) application. 21 U.S.C. § 355.

An NDA, used for pioneering drugs, requires the applicant to submit a full panoply of studies and data to support a safety and effectiveness determination. *Id.* § 355(b)(1). After an NDA is approved, the sponsor lists in FDA's "Orange Book" any patents that cover the drug product or FDA-approved methods of using that drug. *Id.* § 355(b)(1).

An ANDA, used for generic duplicates of existing drugs, relies on all of the safety and effectiveness determinations for the previously approved drug. *Id.* § 355(j). In contrast, a 505(b)(2) application—used for new drugs that are similar but not identical to existing ones—permits the applicant to rely on existing studies for a previously approved drug of the applicant's choosing while supplementing the application with new studies and data to support a safety and effectiveness determination. *Id.* § 355(b)(2).

This case involves the Section 505(b)(2) process. As the district court explained, "new applicants for drug approval [may] rely on research and data that an innovator company generates so long as the new applicant 'references' the innovator's drug and 'certifies' to the innovator's patents." JA21. Thus, when a 505(b)(2) applicant relies on another party's data for a previously approved drug (the "listed drug"), the applicant must address, through a certification process, any patents associated with that drug.

For example, if the 505(b)(2) applicant seeks to market its proposed drug before a patent associated with the listed drug expires, the applicant must provide FDA with a "Paragraph IV certification" for that patent and notify the patentee of the application and grounds for contending that the patent is invalid, unenforceable, or not infringed. 21 U.S.C. § 355(b)(2)(A)(iv). If the patentee sues for infringement within 45 days of receiving that notice, FDA approval is automatically stayed for up to 30 months—which gives the patentee time to try to enjoin the product launch. *Id.* § 355(c)(3)(C), (j)(5)(B)(iii); JA26-31.

FACTUAL BACKGROUND

Colchicine history. The drug colchicine has been used to treat gout for centuries. JA474. In the United States, colchicine has been marketed to treat gout since the 19th century, and it has specifically been used to prevent gout since the 1930s. JA474-75. Early colchicine products were thus available before FDA's modern regulatory approval scheme. For decades, colchicine was legally sold and marketed in the United States by many manufacturers—including Hikma—as an unapproved prescription drug. JA215, JA31-32.

In 1961, FDA first approved a colchicine product, Col-Benemid—a fixed-dose combination product containing colchicine and another drug, pro-benecid. JA475. In 1972, FDA evaluated the effectiveness of Col-Benemid as part of the agency's Drug Efficacy Study Implementation ("DESI") program, and formally confirmed that Col-Benemid effectively treated gout. *Id.* In 1976, FDA approved a generic version of Col-Benemid (Col-Probenecid) relying on its previous approval of Col-Benemid and the DESI finding of effectiveness. *Id.*

Hikma first entered the U.S. colchicine market in 1972 with an unapproved, single-ingredient, 0.6 mg tablet labeled to prevent gout.

JA792. Such tablets were sold by many manufacturers, thus driving the price down to only 4-10 cents per pill. JA962, JA1030. "[M]illions of patients suffering from gout" benefited from this widely available, inexpensive, safe, and effective therapy. JA962.

FDA approval of Colcrys®. This competitive landscape changed after FDA approved the first application filed by Takeda's predecessor (Mutual) in 2009 for a single-ingredient colchicine tablet. JA962. To obtain FDA approval, Takeda submitted 505(b)(2) applications for three colchicine indications: (1) to prevent gout with one or two pills (0.6 mg or 1.2 mg) a day; (2) to treat acute gout flares with two pills (1.2 mg) followed by a third pill (0.6 mg) an hour later; and (3) to treat another condition known as Familial Mediterranean Fever, which is not relevant here.

To support the indication to prevent gout (i.e., prophylaxis treatment), Takeda referenced the previously approved Col-Benemid product and relied on existing literature. That literature taught that colchicine could be dangerous when co-administered with certain drugs, i.e., cytochrome P4503 ("CYP3A4") and Pglycoprotein ("P-gp") inhibitors. Following this teaching, Takeda conducted studies to support a chart in its

label for specific reduced dosing for colchicine when taken with these drugs, thus mitigating harmful drug-drug interactions ("DDIs"). JA478.

To support the indication for treating acute gout flares, Takeda conducted a study (the AGREE trial) that supported using two 0.6 mg pills followed by a third pill an hour later, a dosing regimen that required fewer pills than the standard regimen for treating gout. JA477. After approving Takeda's product for these indications (Colcrys®), FDA required all unapproved colchicine products—including Hikma's—to be taken off the market. Takeda found itself with a monopoly and hiked the price on this centuries-old medicine 50-fold. JA216, JA962.

As the American College of Rheumatology has explained, with low-cost alternatives gone, Takeda created "an extreme cost burden to patients who take colchicine for gout prophylaxis increasing medication cost from approximately $6/month to $300/month." JA962. Insurance companies accustomed to budgeting $1 million for nearly 100,000 colchicine prescriptions annually suddenly had to set aside $50 million per year. JA216. And Takeda's product and 50-fold price increase yielded "no evidence of any meaningful improvement to the public health." JA216, JA973.

Takeda's effort to block Hikma's competing product. Hikma sought to re-launch its colchicine product and filed a 505(b)(2) application for a colchicine tablet identical to Colcrys®. Upon learning of Hikma's application, Takeda filed a citizen petition challenging it on several grounds.

In May 2011, FDA responded to the citizen petition and agreed with Takeda that Hikma must pursue the ANDA pathway for generic drugs if it wished to market a duplicate of Colcrys®, i.e., a 0.6 mg *tablet*. JA473-74. But "FDA denie[d Takeda's] request that any 505(b)(2) application for a single-ingredient oral colchicine product must necessarily cite Colcrys as its listed drug, irrespective of whether the proposed product shares the same strength, pharmacokinetic (PK) profile, or other characteristics such as dosage form or conditions of use." JA474.

Although FDA did not require 505(b)(2) applicants to copy the Colcrys® label, it explained "that product labeling for any single-ingredient oral colchicine product needs to include adequate information on drug-drug interactions, including relevant dose adjustments needed to prevent unnecessary toxicity." *Id.* Additionally, "the labeling for a single-ingredient colchicine product seeking approval for prophy-

laxis of gout flares must inform healthcare providers that the lower dose colchicine regimen evaluated in the AGREE trial is adequate to treat an acute gout flare that may occur during chronic colchicine use." *Id.*

FDA approval of Mitigare®. To address FDA's ruling, Hikma filed a new 505(b)(2) seeking approval for a colchicine *capsule*, which is not a duplicate of Takeda's Colcrys® tablet. It is undisputed that Hikma's 505(b)(2) application did not rely on any Takeda product, research, or data. Takeda Br. 14; Elliott Br. 10-11. Instead, Hikma sought FDA approval solely for the non-patented prophylaxis indication, as permitted by Hatch-Waxman provisions that allow applicants to limit the requested indications to avoid patent protection. *See generally Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1677 (2012) ("FDA acceptance of the carve-out label allows the generic company to place its drug on the market … , but only for a subset of approved uses—i.e., those not covered by the brand's patents.").

To support its label indication for prophylaxis, Hikma—like Takeda—relied on FDA's approval of a prior colchicine product (Col-

Probenecid), which is not associated with any patents, along with the existing literature. Hikma—again, like Takeda—conducted independent studies to address DDIs with colchicine. The results of those studies, however, suggested that the specific dose-reductions to avoid DDIs discussed in the Colcrys® label (and patented by Takeda) may not be appropriate. *See* JA899.

Based on Hikma's DDI studies, FDA determined that it would be appropriate for Mitigare®'s label to contain a more generalized warning that did not include the results of Takeda's DDI studies. "[I]n light of the new information provided by the [Hikma] DDI studies, and the questions about the generalizability of dose modification recommendations, … it was reasonable to forego [*sic*] detailed dose modification recommendations," and "a general precaution to reduce the daily dose and monitor closely for colchicine toxicity is reasonable." JA899.

Based on the existing literature and Hikma's new studies, FDA determined that Mitigare® should be approved without reference to any Takeda data. As FDA explained, "colchicine is a well-known drug and the efficacy and safety of colchicine in gout is well accepted." JA780. FDA added that its "discussants agreed that the clinical pharmacology

data submitted by the applicant are sufficient for approval of this application for colchicine, and a product label can be written based on case reports described in the published literature and the specific clinical pharmacology studies conducted by the applicant." *Id.* Mitigare®'s label thus reads: "[C]oncomitant use of MITIGARE™ and inhibitors of CYP3A4 or P-glycoprotein should be avoided … . If avoidance is not possible, reduced daily dose should be considered and the patient should be monitored closely for colchicine toxicity." JA699.

FDA also found that Hikma's label was safe even though the product was not approved to treat acute gout flares, and the Mitigare® label did not reference Takeda's AGREE test. JA773. As FDA explained, "to the extent that a healthcare provider may be considering use of additional Mitigare for treatment of an acute gout flare in a patient receiving Mitigare for prophylaxis, the review team determined that it would be appropriate for the label to note that Mitigare should not be used in this way, as it has not been studied." *Id.* Hikma's label thus states that "safety and effectiveness of MITIGARE™ for acute treatment of gout flares during prophylaxis has not been studied."

JA698. It further states: "If you have a gout flare while taking MITIGARE, tell your healthcare provider." JA866.

Because Hikma's 505(b)(2) application was supported by published literature and Hikma's own studies—and not any of Takeda's data—FDA approved it in September 2014. In particular, FDA found that Hikma "provided an appropriate patent certification" even though there was no certification to any Takeda patent. JA765, JA780.

Takeda's lawsuits. After learning of FDA's approval, Takeda filed two lawsuits—one against Hikma in Delaware alleging patent infringement, and this suit against FDA alleging violations of the APA.

In the patent case, the district court granted Takeda's request for a temporary restraining order barring Hikma from launching its generic colchicine product. After a hearing on Takeda's motion for preliminary injunction, however, the court found no likelihood of success on the merits and no irreparable harm. The court nonetheless extended the temporary injunction to give Takeda time to file an expedited appeal to the Federal Circuit. *Takeda Pharms.*, 785 F.3d at 627-29.

In the meantime, Takeda also sought to stop Hikma's launch in this case, arguing that (1) FDA should not have approved the applica-

tion for Mitigare® without first requiring Hikma to certify to Takeda's patents, and (2) the FDA-approved label for Mitigare® is unsafe because it omits dose-reduction data from the Colcrys® studies. Elliott, which has a financial interest in Takeda's patents, likewise sued FDA and supplemented Takeda's arguments with a novel statutory construction—namely, that Hatch-Waxman required Hikma to certify to Takeda's patents even if Takeda's data is not relevant to approval. Hikma intervened in both cases, which the district court consolidated. *See* JA1-17 (docket).

On January 9, 2015, the Federal Circuit heard oral argument in the patent case and, just a few hours later, summarily affirmed the Delaware district court and lifted the temporary injunction, noting that an opinion would follow. Case 15-1139, Dkt. 72. Later that day, the district court in this case denied Takeda's and Elliott's permanent injunction and summary judgment motions. Dkt. 68. Hikma immediately launched Mitigare® and an authorized generic, providing patients with the first FDA-approved, single-ingredient generic colchicine product.

A few days later, on January 12, 2015, the district court issued a 77-page published decision rejecting Appellants' arguments and holding that FDA did not act arbitrarily or capriciously when it approved Hikma's 505(b)(2) application. Dkt. 74. This appeal followed.

On May 6, 2015, before Appellants filed their opening briefs, the Federal Circuit issued a 2-1 published decision holding that, under the legal standard for induced infringement, Takeda is not entitled to an injunction because its patent claims are unlikely to succeed on the merits. 785 F.3d at 630. Takeda unsuccessfully sought rehearing en banc. Case No. 15-1139, Dkt. 87 (Fed. Cir. Aug. 19, 2015).

SUMMARY OF ARGUMENT

I. The district court properly held that the FDA did not act arbitrarily or capriciously when it approved Hikma's 505(b)(2) application for Mitigare® without requiring certifications to Takeda's patents, because the application did not rely on Colcrys® or any Takeda data. Elliott (but not Takeda or its amicus, PhRMA) argues that Hatch-Waxman and FDA's implementing regulations do not require such a *quid pro quo* for method patents, and thus Hikma had to certify to Takeda's method patents regardless of whether Hikma's application re-

lied on Takeda data. But the statute and regulations confirm the district court's conclusion "that Elliott's reading is a distortion of the statutory text, rather than a statement of its unambiguous plain meaning." JA84.

Instead of joining Elliott's meritless statutory argument, Takeda argues that FDA should have rejected Hikma's application because *FDA* purportedly relied on Takeda's data to support the Mitigare® approval. But this argument misconstrues the administrative record and essentially seeks reconsideration of FDA's citizen petition ruling rejecting Takeda's argument that "any single-ingredient colchicine product submitted through the 505(b)(2) pathway must necessarily cite Colcrys as its listed drug." JA474. FDA consulted Takeda's studies only to understand why its results differed from Hikma's studies, an analysis ultimately leading to FDA's rational conclusion that Hikma's product is safe without Takeda's data. JA899.

II. The district court also properly held that FDA did not arbitrarily or capriciously ignore its prior citizen petition ruling or otherwise approve an unsafe label for Mitigare® that omits certain specific dosing information contained in Colcrys® label. FDA expressly "considered"

its citizen petition ruling and rationally explained its decision to approve a Mitigare® label with DDI warnings that differed from the Colcrys® label. JA899. FDA further explained why the Mitigare® label is safe even though it does not mention dosing for acute gout flares. JA773.

The district court's judgment should be affirmed.

STANDARD OF REVIEW

"On appeal from the district court's grant of summary judgment," this Court "review[s] [the agency's] decision *de novo*, applying the familiar APA standard, which requires [the Court] to set aside agency action that is 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." *Jicarilla Apache Nation v. U.S. Dep't of Interior*, 613 F.3d 1112, 1118 (D.C. Cir. 2010) (quoting 5 U.S.C. § 706(2)(A)). The "arbitrary and capricious" standard is "narrow" and "highly deferential" —it "presumes the agency's action to be valid," "forbids a court from substituting its judgment for that of the agency," and "mandates judicial affirmance if a rational basis for the agency's decision is presented, even though [the Court] might otherwise disagree." *Envtl. Def. Fund,*

Inc. v. Costle, 657 F.2d 275, 283 (D.C. Cir. 1981) (internal citation omitted).

Moreover, when examining a "scientific determination," the "reviewing court must generally be at its most deferential." *Baltimore Gas & Elec.*, 462 U.S. at 103; *accord Int'l Fabricare Inst. v. EPA*, 972 F.2d 384, 389 (D.C. Cir. 1992). The Court "must look at the decision not as the chemist, biologist or statistician that [it is] qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality." *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976) (en banc).

Under *Chevron*'s first step, a statute's meaning is a legal question reviewed *de novo*. *Chevron, USA, Inc. v. NRDC, Inc.*, 467 U.S. 837, 842-43 (1984). Under *Chevron*'s second step, where a statute is ambiguous, an agency's reasonable interpretation is entitled to deference. "[I]t is not for the court to choose between competing meanings of an ambiguous statute." *Teva Pharm. USA, Inc., v. FDA*, 441 F.3d 1, 4 (D.C. Cir. 2006) (internal quote marks omitted).

ARGUMENT

I. FDA was not required to reject Hikma's 505(b)(2) application because it omitted certifications to Takeda's patents.

Although they offer different arguments, both Elliott and Takeda argue that FDA should have rejected Hikma's 505(b)(2) application because it did not certify to Takeda's Colcrys® patents. The district court properly rejected these arguments under both *Chevron* steps. JA52-85.

A. The district court properly rejected Elliott's reading of Hatch-Waxman.

According to Elliott alone, Hatch-Waxman requires 505(b)(2) applicants to certify to any "applicable" method patents in the Orange Book —regardless of whether the applicant relies on the listed drug associated with that patent. Elliott Br. 18. As the district court recognized, this unprecedented construction ignores the statutory text and the *quid pro quo* established by Congress. JA72-85.

1. Hatch-Waxman requires certifications only to patents associated with a listed drug referenced in the 505(b)(2) application.

As the district court explained, "Congress' intent regarding the scope of a Section 505(b)(2) applicant's patent certification obligation is clear on the face of the statute: such applicant need only certify to the product patents or the method-of-use patents that are associated with

the reference listed drug (*i.e.*, the drug product on whose investigations the 505(b)(2) applicant relies)." JA75. This reading is consistent with the *quid pro quo* required by Hatch-Waxman. That is, "new applicants for drug approval [may] rely on research and data that an innovator company generates so long as the new applicant 'references' the innovator's drug and 'certifies' to the innovator's patents." JA21.

Elliott's contrary arguments ignore basic English usage and distort the statutory text. The relevant portion of Section 505(b)(2)(A) requires a patent certification only for each patent claiming "a drug … relied upon by the applicant for approval," or "a use for *such* drug":

> (2) An application submitted under paragraph (1) for *a drug* for which the investigations described in clause (A) of such paragraph and *relied upon by the applicant for approval* of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include—
>
> > (A) *a certification*, in the opinion of the applicant and to the best of his knowledge, *with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval* under this subsection….

21 U.S.C. § 355(b)(2)(A) (emphasis and arrows added).

Under a plain reading of this provision, the statute requires "a certification … with respect to each patent which claims" (1) "*the drug*," i.e., a patent covering the listed drug product "relied upon by the [505(b)(2)] applicant for approval"; or (2) "a use for *such drug*," i.e., a method patent covering a use for the listed drug if the applicant "is seeking approval" for that use. *Id.* (emphasis added). This is precisely how the district court read the statute in rejecting Elliott's argument under *Chevron*'s first step. JA75. Elliott's contrary reading is meritless.

a. Elliott badly misconstrues the term "such drug." Elliott concedes that the statutory terms "a drug" and "the drug" refer to the *drug product* referenced in the 505(b)(2) application (here, Col-Probenecid). Elliott Br. 24. But according to Elliott, the term "such drug" refers to something entirely different: the *active drug substance* for which the applicant seeks approval (here, colchicine). *Id.* It thus follows, the argument goes, that Hikma needed to search the entire Orange Book for any method patents potentially "applicable" to the application, regardless of whether those patents are associated with the drug product referenced in the application. *Id.* at 18. Not so.

"A standard principle of statutory construction provides that identical words and phrases within the same statute should normally be given the same meaning." *Powerex Corp. v. Reliant Energy Servs., Inc.*, 551 U.S. 224, 232 (2007). "That maxim is doubly appropriate" where, as here, the words or phrases were inserted at the same time. *Id.* And as the district court held, "[a]lthough the term 'drug,' as used in the FDCA, can refer to both the finished drug product and also its active ingredient, *see* 21 U.S.C. § 321(g)(1), the fact that Congress repeated the word 'drug' twice within such a short span of text strongly suggests that it intended the *same* definition to apply to that term." JA78. Indeed, the presumption that a given term means the same thing throughout a statute is "surely at its most vigorous when a term is repeated within a given sentence." *Brown v. Gardner*, 513 U.S. 115, 118 (1994).

As the district court further explained, "[t]he fact that Congress uses the phrase '*such* drug' after the conjunction further indicates its intent to reference only *one* drug—the drug for which the relied-upon investigations were conducted—in section (b)(2)(A)." JA78. In support, the court explained, "[t]he term 'such,' when used as an adjective, is an inclusive term, showing that the word it modifies is part of a larger

group." JA78 (citations omitted). "As much as Elliott may wish that Congress had employed another article in the method-of-use clause of subsection (b)(2)(A), Congress selected 'such,' and this Court is required to take Congress at its word." JA79.

b. Elliott incorrectly argues that the adjectival phrase "for which the applicant is seeking approval" must modify the word "drug" as "the *nearest* reasonable referent." Elliott Br. 25-26. Again, the statute requires a certification for each patent "which claims a use for such drug for which the applicant is seeking approval." The phrase "for which the applicant is seeking approval" modifies the entire term "a use for such drug." In other words, the applicant must certify to a method patent associated with the listed drug *only* if the application seeks approval for the use of the listed drug covered by that patent.

This interpretation hardly "renders 505(b)(2)(B) superfluous." Elliott Br. 26 Subsection (b)(2)(B) requires a separate representation by the applicant if "a method of use patent does *not* claim a use [for the listed drug] for which the applicant is seeking approval[.]" 21 U.S.C. § 355(b)(2)(B) (emphasis added). In other words, when the application relies on a previously approved "drug for which investigations … were

conducted," the applicant must certify under Section 505(B)(2)(A) to any method patents if "the applicant is seeking approval" for "a use for such drug" covered by that patent. Alternatively, if appropriate under Section 505(b)(2)(B), the applicant can represent that "the method of use patent does not claim a use for which the applicant is seeking approval."

c. Because the statute is unambiguous, "reliance on legislative history is unnecessary." *Mohamad v. Palestinian Auth.*, 132 S. Ct. 1702, 1709 (2012). Nevertheless, the legislative history essentially mirrors the statute, and thus provides no basis to distort the statute's clear text.

Relying on a single House Committee Report, Elliott suggests that the Committee explained that "the applicant must certify" with respect to "all product patents which claim the listed drug and *all use patents which claim an indication for the drug for which the applicant is seeking approval*." Br. 27 (quoting H.R. Rep. No. 98-857, pt. 1 at 32 (1984) ["House Report"]). But that House Report language merely replaces the word "use" from Section 505(b)(2)(A) with the word "indication." Thus, as the district court explained, "the House report says no more than

what the statute states." JA82 n.23. In fact, Takeda has cherry-picked statements from that report, ignoring others that link patent certifications—including certifications for method patents—to "the listed drug" relied upon in the application. *Id.* (quoting House Report at 32).

In short, the Hatch-Waxman "*quid pro quo* arrangement is preserved if subsection (b)(2)(A) is interpreted as it was written—to require a new drug applicant to certify to the product and method-of-use patents that are related to the drug the applicant references and relies upon for approval." JA82. As Hikma did not rely on Colcrys® for approval (JA833), the statute did not require it to certify to the Colcrys® patents. In arguing otherwise, "Elliott has cast aside all of the very clear textual indications" and created "a distortion of the statutory text, rather than a statement of its unambiguous plain meaning." JA84.

2. Even if the statute were ambiguous, FDA's interpretation would get *Chevron* deference.

As discussed, Hatch-Waxman unambiguously links all patent certifications to the listed drug relied upon by the 505(b)(2) applicant, thus defeating Elliott's statutory argument under *Chevron*'s first step. But as the district court recognized, even if the statute were ambiguous, it was "entirely reasonable for FDA to interpret the certification provision

in subsection (b)(2)(A) to require a Section 505(b)(2) applicant to certify only to the product and use patents that claim the reference listed drug, which, according to FDA, has been its long-held view of the statute." JA84.

Elliott challenges this conclusion by arguing that, if the statute were deemed ambiguous, FDA's regulations would control—and they purportedly require Hikma's approval to be rescinded. Not so.

The regulations, like the legislative history, merely mirror the statute. According to the regulation: "If the labeling of the drug product for which the applicant is seeking approval includes an indication that … is claimed by a use patent, the applicant shall submit an applicable certification under paragraph (i)(1)(i) of this section." 21 C.F.R. § 314.50(i)(1)(iii)(B). According to Elliott, the phrase "claimed by a use patent" refers to any use patent in the Orange Book—regardless of whether it is associated with the listed drug relied upon in the 505(b)(2) application.

But the regulations, like the statute, link patent certifications (including for method patents) to the listed drug "relied upon by the applicant for approval":

> *Patent claiming* drug, drug product, or *method of use.*
>
> Except as provided in paragraph (i)(2) of this section, *a certification with respect to each patent … that … claims a drug* (the drug product or drug substance that is a component of the drug product) *on which investigations that are relied upon by the applicant for approval* of its application were conducted *or that claims an approved use for such drug* and for which information is required to be filed under section 505(b) and (c) of the act and 314.53.

21 C.F.R. § 314.50(i)(1)(i) (emphasis added). As with the statute, the applicant must certify to a method patent "that claims an approved use for such drug"—i.e., the listed drug product "on which investigations that are relied upon by the applicant for approval" were conducted.

While "Elliott reads this regulation to mean that it is FDA's policy that all method-of-use patents claiming the same indication as the applicant's drug must be certified to," the district court properly concluded that "that is not what the regulation says." JA85 n.25. "[I]ndeed, consistent with [Hatch-Waxman], FDA has long maintained that the only 'applicable' patent certifications are those that are made in relation to product or use patents that claim the reference listed drug." JA85 n.25; *see also* JA645-47, 650.

Again, FDA's long-standing reading of the statute is entitled to *Chevron* deference. 467 U.S. at 842-43. This presumably explains why

neither Takeda nor its amicus supports Elliott's tortured statutory interpretation.

B. The district court properly rejected Takeda's argument that Colcrys® data was necessary for approval.

Instead of adopting Elliot's flawed interpretation of Hatch-Waxman, Takeda argues that FDA should have rejected Hikma's application because the administrative record shows that FDA relied on Colcrys® data to approve Mitigare®. But this argument misconstrues both the 505(b)(2) process and the administrative record.

1. Properly applying 505(b)(2), Hikma chose its listed drug, and FDA found Hikma's information sufficient to support approval.

According to Takeda, there was a "yawning gap in Hikma's 505(b)(2) application," because "Hikma quite intentionally omitted any citation to Colcrys." Takeda Br. 17. This argument is meaningless, because FDA found that Takeda's Colcrys® data was not necessary for approval. *See* JA833-34, 894-899. As explained below, Hikma properly followed the 505(b)(2) process when it submitted an application that "omitted any citation to Colcyrs." Takeda Br. 17.

a. The Court should dismiss out-of-hand Takeda's threshold argument that FDA policy "required 505(b)(2) applicants to 'choose the

listed drug or drugs that are *most similar* to the drug for which approval is sought.'" Takeda Br. 19. No such policy exists. Indeed, as discussed, FDA previously rejected Takeda's argument that "any single-ingredient colchicine product submitted through the 505(b)(2) pathway must necessarily cite Colcrys as its listed drug." JA670; *see* JA52-53.

Takeda cites an FDA citizen petition ruling noting that an "applicant should choose the listed drug or drugs that are most similar to the drug for which approval is sought." JA648. But in that same ruling, FDA went on to say that "neither the statute, the regulations, nor the Draft Guidance directly addresses how to identify the listed drug or drugs on which a 505(b)(2) applicant is to rely." *Id.* And in a later citizen petition ruling, FDA clarified that the applicant—not FDA—determines what drug is most appropriate: "a *sponsor interested in submitting a 505(b)(2) application* that relies upon FDA's finding of safety and/or effectiveness for one or more listed drugs *should determine which listed drug(s) is most appropriate for its development program*." JA658 (emphasis added); JA68.

Takeda also cites an FDA form questioning whether the proposed product is a "pharmaceutical equivalent" or a "pharmaceutical alterna-

tive." JA835. But this form does not require FDA to second-guess the applicant's choice for the listed drug (assuming it is not a duplicate product that must be submitted via the ANDA process). *Id.*

As the district court properly held, therefore, the "most similar" standard "does not reflect"—and, in fact, never reflected—"a statutory or regulatory requirement." JA67-68. Hikma thus had every right to choose Col-Probenecid instead of Colcrys® as "most appropriate for its development program" given that the former product is not associated with any patents. Takeda's contrary argument lacks merit.

To be sure, in choosing to rely on Col-Probenecid, Hikma needed to convince FDA that this listed product, along with the literature and the company's independent testing, was sufficient to justify approval under 505(b)(2). As FDA has explained, "a 505(b)(2) applicant seeking approval for a change to a listed drug [must] supply information sufficient to support the change proposed," and "it follows that the more similar a proposed drug is to the listed drug cited, the smaller the quantity of data that will be needed to support the proposed change." JA648. There is "a direct correlation between the drug the applicant chooses to reference and the applicant's burden of proof." JA68.

b. In evaluating whether an applicant's data are sufficient to support a finding of safety and effectiveness under 505(b)(2), as here, FDA is free to access all available knowledge. Where a study reaches results different from prior similar studies, for example, it is only common sense for FDA to *compare* those studies to evaluate whether the applicant's new study is rigorous, credible, and explainable. Not surprisingly, therefore, the district court held that "Takeda fails entirely to explain its suggestion that [the] statutory language can somehow be read to bind *FDA* in its consideration of data pertinent to a submitted application." JA57. Further, "the statute says nothing about the circumstances under which FDA can, or cannot, consult third-party data when it makes a scientific determination regarding whether or not to approve a Section 505(b)(2) application." *Id.*

If FDA decides, based on studies for a drug not referenced in the application, that additional information is necessary to support approval, the proper response is to reject the application. *See* JA338. The applicant must then decide how to address that rejection—for example, by referencing a different drug, or conducting more studies. Takeda points

to no statute, regulation, or policy that actually would have required FDA to force Hikma to reference Colcrys®.

c. After reviewing the available information, FDA found that Hikma met its burden, because the information it submitted—which, again, included no Takeda data—showed that Mitigare® is sufficiently safe and effective to prevent gout. In its approval explanation, FDA explained that "colchicine is a well-known drug and the efficacy and safety of colchicine in gout is well accepted." JA 780. The report added that FDA's "discussants agreed that the clinical pharmacology data submitted by the applicant are sufficient for approval of this application for colchicine, and a product label can be written based on case reports described in the published literature and the specific clinical pharmacology studies conducted by the applicant." *Id.*

2. Colcrys® data was not essential to Hikma's approval.

Takeda also argues that FDA should have rejected Hikma's application because the administrative record purportedly shows that "Colcrys data was necessary to FDA's approval of Mitigare." Takeda Br. 16. The record shows no such thing.

True, FDA consulted Colcrys® data when reviewing Hikma's application, but only to assess why the DDI data from the different applications showed different results. In other words, FDA did its job—it needed to ensure that the information supplied by Hikma was sufficient to justify approval.

As the district court explained: "The fact that FDA considered the differences between what West-Ward's clinical studies found and what Mutual's clinical studies had concluded does not necessarily mean that West-Ward's own submissions had failed to show that Mitigare is safe and effective for the prophylaxis of gout independently of the Colcrys® data. *In fact, FDA specifically stated that, based on [Hikma's] submissions alone, the agency had come to the conclusion that Mitigare is safe and should be approved*." JA65 (emphasis added). In support, the court cited FDA's explanation that "the clinical pharmacology data submitted by [Hikma] are sufficient for approval of this application for colchicine, and a product label can be written based on case reports described in the published literature and the specific clinical pharmacology studies conducted by the applicant." *Id.* (quoting JA780); *see also id.* (quoting

JA770 ("No clinical pharmacology/biopharmaceutics deficiencies were identified in the original application for [Mitigare.]")).

The Mitigare® label confirms the district court's analysis. The label contains no reference to the patented dosing regimens found on the Colcrys® label for treating acute gout flares, or for co-administering colchicine with certain other drugs to avoid DDIs. Indeed, Takeda points to nothing in the Mitigare® label that comes from Colcrys® data. As FDA determined, everything in Hikma's label is supported by *its* application.

The district court thus properly concluded that, "from the standpoint of the type of reliance that Section 505(b)(2) requires and that Congress clearly cares about, FDA did not 'rely' on Mutual's Colcrys studies to fill in an identified gap in the safety and effectiveness studies that [Hikma] submitted with its application for Mitigare, as would ordinarily be the case when a Section 505(b)(2) applicant exercises its right of reliance on such studies under the statute." JA65. And as the district court recognized, FDA's conclusion that Mitigare®, standing on Hikma's application alone, was safe and effective, is a "scientific deter-

mination" that is entitled to the "most deferential" review from this "reviewing court." *Baltimore Gas & Elec.*, 462 U.S. at 103.

Takeda's citations of examples from the administrative record do not further its cause. According to Takeda, "FDA's labeling decisions relied heavily on the previously approved Colcrys label. The Office of Prescription Drug Promotion repeatedly compared the proposed Mitigare package insert to the approved Colcrys insert and raised concerns based on any discrepancies." Br. 21. But after comparing and analyzing the relevant data, FDA ultimately concluded that such concerns did not require Hikma to include the specific dosing contained in the Colcrys® label. JA899.

Nor is there any basis to Takeda's other arguments—that "FDA expressly 'referenced Colcrys Medication Guide, most recently revised 7/2011 as a comparator where applicable'"; that "FDA created several charts lining up Colcrys data and Mitigare data"; and that FDA "analyz[ed] differences between Mutual's and Hikma's drug-drug interaction studies." Takeda Br. 22. Comparing data does not mean the Colcrys® data were necessary to support Hikma's approval. On the contrary, FDA even considered "whether the Colcrys labeling should be revised,"

but ultimately determined that "either approach"—i.e., the Mitigare® or the Colcrys® label—"could be considered reasonable." JA899.

Next, Takeda argues that FDA "studied data for both Colcrys and Mitigare and ultimately concluded that '[Hikma's] and Mutual's DDI *data combined*, suggests that P-gp inhibition may play a more dominant role than CYP3A4 inhibition.'" Takeda Br. 22 (quoting JA928). But as the district court noted, that statement "does not appear to be about the safety of Mitigare or Colcrys at all, but is a statement about *the nature of P-gp and CYP3A inhibitors*, in light of what, combined, the Colcrys and Mitigare data showed." JA66 n.17. In other words, "FDA was not expressing the agency's concerns or doubts about [Hikma's] submissions regarding the safety of Mitigare, but instead was merely *comparing* the two different sets of data results that the two different colchicine products had generated about the potential interaction of 0.6 mg of colchicine with the same two classifications of drugs." *Id.*

Takeda further argues that "the approved Mitigare label does not merely dispense with the Mutual warnings; it cautions against the co-administration of Mitigare and P-gp or CYP3A4 inhibitors—warnings consistent with [*Takeda's*] studies but not with Hikma's." Br. 23. The

warnings, however, are consistent with both companies' studies. And the DDI interactions against which Mitigare®'s label warns were "based on the case reports in the literature," which contains warnings virtually identical to those in the Mitigare® label. JA899.

In short, Hikma's application did not rely on Colcrys® for approval. FDA did not fill any evidentiary gaps in Hikma's application with Colcrys® data. And nothing in the Mitigare® label comes from the Colcrys® label. As the district court correctly held, "from the standpoint of the type of reliance that Section 505(b)(2) requires and that Congress clearly cares about, FDA did not 'rely' on Mutual's Colcrys studies to fill in an identified gap in [Hikma's] safety and effectiveness studies." JA65. Thus, FDA's decision to approve Hikma's application without requiring a certification to Takeda's patents was, at a bare minimum, "rational"—and it was certainly not arbitrary or capricious. *Envtl. Def. Fund*, 657 F.2d at 283.

C. Given that the Federal Circuit denied injunctive relief, Appellants cannot justify their requested relief.

Appellants seek to rescind FDA approval to give Takeda an opportunity to enforce its patents and enjoin Hikma's launch. But Takeda already got that opportunity—and it lost.

In rejecting Takeda's request for injunctive relief, both the District of Delaware and the Federal Circuit held, as a matter of law, that Mitigare®'s labeling does not induce infringement of the Coclrys® patents. *See* 785 F.3d at 632 ("Given the statutory scheme explained above, vague label language cannot be combined with speculation about how physicians may act to find inducement."); *id.* at 634 (the "label language failed to recommend or suggest to physicians that the patented DDI methods should be followed"). En banc review was denied, thus essentially ending Takeda's chance to rely on patent rights to exclude Mitigare® from the market. Rescinding FDA approval for Mitigare® would not only conflict with Hatch-Waxman, the regulations and FDA policy—it would pointlessly provide Takeda with windfall exclusivity. Appellants make no effort to argue otherwise.

II. FDA did not arbitrarily or capriciously depart from a prior citizen petition ruling, or otherwise approve an unsafe label for Mitigare®.

Nor is there any support for Takeda's arguments that Mitigare®'s label arbitrarily and capriciously departed from a prior FDA citizen petition by omitting specific DDI and acute gout flare dosage information for colchicine contained in the Colcrys® label. As shown below, FDA ra-

tionally explained its decision to approve the Mitigare® label without this information, and that decision is entitled to the highest level of deference.

A. FDA expressly "considered" and addressed its prior citizen petition ruling addressing DDIs.

Takeda first argues that FDA's labeling for Mitigare® violated the APA because it lacks critical safety information with regard to DDIs. As discussed, the Colcrys® label contains a chart with specific dose reductions when combined with certain drugs. JA134-35. In contrast, the Mitigare® label contains stern warnings without any specific dose adjustments, such as: "[C]oncomitant use of MITIGARE™ and inhibitors of CYP3A4 or P-glycoprotein] should be avoided.... If avoidance is not possible, reduced daily dose should be considered and the patient should be monitored closely for colchicine toxicity." JA626.

Takeda argues that FDA's decision to allow Hikma to omit specific dose-reduction DDI information from its label arbitrarily and capriciously departed from FDA's prior citizen petition ruling. There, FDA said that "product labeling for any single-ingredient oral colchicine product needs to include *adequate information* on drug-drug interac-

tions, including *relevant dose adjustments* needed to prevent unnecessary toxicity." JA670 (emphasis added); Takeda Br. 26.

Yet, Takeda glosses over the fact that FDA expressly "*considered* the [Mitigare®] labeling in light of FDA's earlier consideration of drug-drug interaction information for colchicine in the context of a citizen petition submitted by Mutual in 2010." JA899 (restating relevant portion of citizen petition ruling). FDA noted that Hikma's DDI findings "suggest that the results are highly variable from one CYP3A4 inhibitor to another, or from one P-gp inhibitor to another," and that therefore "it may not be appropriate to recommend precise dose modifications." JA779. Indeed, FDA also "noted that the Colcrys dose modification recommendations were not tested clinically and the Colcrys labeling could be misleading if interpreted to mean that following dose modification instructions would avoid a problem." JA899.

FDA then rationally explained why information in Hikma's label was adequate to support approval of the prophylaxis indication:

> [*I*]*n light of the new information provided by the* [*Hikma*] *DDI studies, and the questions about the generalizability of dose modification recommendations, the regulatory briefing panel opined that it was reasonable to forego* [sic] *detailed dose modification* recommendations and include Warnings and Precautions about drug interactions with

> colchicine based on the case reports in the literature, which suggest that dual inhibitors of CYP3A4 and P-gp are particularly problematic when administered with colchicine, and co-administration should be avoided. *If avoidance is not possible, a general precaution to reduce the daily dose and monitor closely for colchicine toxicity is reasonable, given the uncertainty about generalizability and variability among individuals.*

JA899 (emphasis added); *see also* JA766 (finding "general recommendation for avoidance" to be "justifiable").

Takeda reads the citizen petition ruling as compelling FDA to require Hikma to copy the dose information from the Colcrys® label. But as the district court explained, "it cannot reasonably be asserted that [the citizen petition ruling] established an agency policy that the labels for single-ingredient oral colchicine products *must* contain *all* of the drug-drug interaction information that appears on the Colcrys label." JA86.

As a practical matter, therefore, Takeda asks this Court to second-guess FDA's determination that Hikma's general warnings are "reasonable" and otherwise safe. This "scientific determination" lies at the core of FDA's particular expertise and is entitled to the "most deferential" review from the courts. *Baltimore Gas & Elec.*, 462 U.S. at 103; *Int'l Fabricare Inst.*, 972 F.2d at 389.

B. FDA rationally omitted acute gout flare dosing information from the Mitigare® label.

As a final argument, Takeda asserts that FDA arbitrarily and capriciously departed from its earlier citizen petition ruling by omitting from the Mitigare® label acute gout flare dosing information from the AGREE trial. Once again, Takeda is wrong.

As discussed, FDA had previously said—based on the record then before the agency—that "the labeling for a single-ingredient colchicine product seeking approval for prophylaxis of gout flares must inform healthcare providers that the lower dose colchicine regimen evaluated in the AGREE trial is adequate to treat an acute gout flare that may occur during chronic colchicine use." JA670. But FDA faced a different record when it considered Hikma's 505(b)(2) application for the Mitigare® capsule.

To support its application, Hikma submitted testimony and evidence to support omitting information from the AGREE trial about treating acute gout flares from the Mitigare® labeling, which was limited to the prophylaxis indication. *See* JA1025-26. As Hikma's experts explained, "limitations on the AGREE trial"—which was conducted for *acute* gout flare patients—"preclude any meaningful extrapolation of its

results, other than its safety findings, to the *chronic* setting." JA1025 (emphasis added). That is because the AGREE trial "excluded patients taking colchicine prophylactically" and "only evaluated pain for twenty-fours, when a flare of gout will often last for several consecutive days." *Id.*

FDA considered these submissions and concluded: "Although the applicant is not seeking an indication for the treatment of acute gout flares, to the extent that a healthcare provider may be considering use of additional Mitigare for treatment of an acute gout flare in a patient receiving Mitigare for prophylaxis, the review team determined that it would be appropriate for the label to note that Mitigare should not be used in this way, as it has not been studied." JA773.

The Mitigare® label thus contains a limitation disclaimer to this effect. JA699. The accompanying medication guide further states: "If you have a gout flare while taking MITIGARE™, tell your healthcare provider." JA866. FDA did not address the propriety of either of these labeling instructions in its citizen petition ruling, and its decision to use these instructions for Mitigare® was, at a minimum, "rational." *Envtl. Def. Fund*, 657 F.2d at 283.

Notably, Takeda does not (and cannot) argue that the Mitigare® label is unsafe. After all, the Mitigare® label expressly sets a "maximum dose" of just "1.2 mg/day"—an admittedly safe daily dosage amount that is less than the minimum dose required to treat acute gout flares (1.8 mg in an *hour*). *Compare* JA698, *with* JA477. As the district court put it, "the agency came to the utterly rational conclusion that a label with the lower-dose [acute flare] instructions was not only unwarranted, it might also confuse users into taking more Mitigare than the recommended daily dosage, exposing them to greater risk of harm." JA90 (quoting JA773).

In short, the district court rightly concluded that "the record clearly reflects the agency's well-reasoned and well-supported rationale for reaching this conclusion." JA90. Even if an agency changes positions, it "need not demonstrate to a court's satisfaction that the reasons for the new policy are *better* than the reasons for the old one; it suffices that the new policy is permissible under the statute, that there are good reasons for it, and that the agency *believes* it to be better, which the conscious change of course adequately indicates." *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009). And again, FDA's "scientific

determination" lies at the core of its expertise and is entitled to a "most deferential" review from the courts. *Baltimore Gas & Elec.*, 462 U.S. at 103.

CONCLUSION

For the foregoing reasons, this Court should affirm the district court's judgment.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on October 16, 2015, I filed the foregoing BRIEF via the Court's ECF filing system, and caused it to be served electronically to the registered participants as identified on the Notice of Electronic Filing:

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CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure ("FRAP") 32(a)(7)(B) and the Court's July 1, 2015 Scheduling Order because:

   This brief contains 8,738 words, excluding the portions exempted by FRAP 32(a)(7)(B)(iii).

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