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No. 15-5021 (consolidated with No. 15-5022)

IN THE

United States Court of Appeals for the District of Columbia Circuit

TAKEDA PHARMACEUTICALS U.S.A., INC.,

Plaintiff-Appellant,

v.

SYLVIA MATHEWS BURWELL, IN HER OFFICIAL CAPACITY AS SECRETARY, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, *ET AL.*,

Defendants-Appellees,

and

HIKMA PHARMACEUTICALS PLC, *ET AL.*,

Intervenor-Appellees.

On Appeal from the
United States District Court for the District of Columbia
Case No. 1:14-cv-1668 (Hon. Ketanji Brown Jackson)

REPLY BRIEF FOR APPELLANT TAKEDA PHARMACEUTICALS U.S.A., INC.

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October 30, 2015

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TABLE OF AUTHORITIES

* Authorities upon which we chiefly rely are marked with asterisks.

GLOSSARY

ANDA: Abbreviated New Drug Application

CYP3A4: Cytochrome P450 3A4

FDA: Food and Drug Administration

NDA: New Drug Application

P-gp: P-glycoprotein

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STATUTES & REGULATIONS

All applicable statutes and regulations are contained in Takeda's opening brief.

INTRODUCTION & SUMMARY OF ARGUMENT

The first page of the response briefs for FDA and Hikma is telling. Hikma praises FDA's efforts to approve its colchicine drug, Mitigare, because the approval supposedly brought "[r]elief" to the colchicine market. Hikma Br. 1. FDA, meanwhile, characterizes Takeda's suit as a competitor's effort "to keep Mitigare off the market." FDA Br. 1. The message in both briefs is clear: It was good for the colchicine market to allow Mitigare to compete with Takeda's colchicine drug, Colcrys.

But Congress did not give FDA authority to grant approvals based on FDA's impression of the marketplace. Congress performed that policy balancing itself, and enacted the Hatch-Waxman Amendments to implement it. The Hatch-Waxman scheme extracts concessions from both components of the prescription-drug market; generic drug manufacturers may borrow safety data from other approved drugs to support their own applications, but in that event innovator drug manufacturers may enforce their patent rights. *See* 21 U.S.C. § 355(b)(2). FDA departed from that statutory scheme here. It allowed Hikma to leverage Takeda's safety data—but refused to enforce the patent certification obligations that would have provided Takeda with notice of Hikma's application and an opportunity to secure a stay of FDA approval pending resolution of a patent proceeding.

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FDA responds that it was entitled to use Colcrys data to approve the Mitigare application, just so long as *it* (and not Hikma) identified Colcrys. *See* FDA Br. 26-29. That coy distinction does not square with the text of the statute. The statute does not turn on whether an applicant wrote another drug's name on a form; it asks whether another drug's data is "relied upon by the applicant for approval of the application." 21 U.S.C. § 355(b)(2). Whether FDA or the applicant names the previously approved drug, the applicant is the ultimate beneficiary either way. Indeed, before this case, FDA consistently applied an interpretation of "reliance" identical to Takeda's interpretation here. Its brief fails to even attempt to distinguish some of its prior statements, and does not meaningfully distinguish others.

The real question about reliance, then, is whether Colcrys data was necessary to FDA's approval of Mitigare. Although FDA claims in the alternative that it was not, *see* FDA Br. 29-33, the record belies that claim. [redacted] JA928. The agency's post hoc explanation that it was merely comparing data for comparison's sake rings hollow.

Finally, FDA argues that its approval of Mitigare, as currently labeled, is consistent with prior agency statements about dose adjustments and a low-dose

colchicine regimen. On the dose adjustments, FDA repeats the point that the potential for dangerous drug-drug interactions might not be generalizable from one drug to the next. *See* FDA Br. 40-43. Try as it might, though, the agency never offers a record-supported explanation for excluding *all* dose adjustments when its generalizability concerns cast doubt only on *some*. FDA similarly repeats the rationale that information about a low-dose colchicine regimen was left off the Mitigare label because Mitigare was approved for prophylaxis, not treatment of acute gout flares. *See* FDA Br. 44-46. But the agency ignores its prior unequivocal statements that information about a low-dose regimen is necessary for *both* indications.

FDA short-circuited the statute by allowing Hikma to omit required patent certifications, and it departed from its own past policies without reasoned explanation. The approval of Mitigare was arbitrary, capricious, and contrary to law on both scores.

The District Court's decision should be reversed.

I. TAKEDA'S PATENT CLAIMS DEPEND IN PART ON THE RESOLUTION OF THIS APA CHALLENGE.

To begin—and to erase any doubt—this APA challenge matters. Hikma suggests that Takeda's patent claims have "essentially end[ed]" and that this Court's decision on Takeda's APA claims will be "pointless[]." Hikma Br. 40. Far from it.

First, the patent proceedings have not yet concluded. A Delaware district court denied Takeda's motion for a preliminary injunction, and the Federal Circuit affirmed in a divided decision. *See Takeda Pharms. v. West-Ward Pharm. Corp.*, 785 F.3d 625 (Fed. Cir. 2015). The Federal Circuit reviewed the denial of a preliminary injunction only for abuse of discretion, *id.* at 629, and considered whether Hikma had raised a "substantial question" about infringement at the preliminary injunction stage, *id.* at 630. Those are not final merits decisions. In fact, the Hatch-Waxman notice requirement sidestepped by FDA here would have enabled Takeda to litigate its patent rights without resorting to an emergency motion on an incomplete and rushed record. The parties are now briefing dispositive motions in the Delaware district court.

Second, the substance of Takeda's patent claim in the Delaware court depends in part on this Court's resolution of the multiple APA challenges raised here. In this case, Takeda has argued that FDA deviated from prior policy without a reasoned explanation and that it should have required the Mitigare label to provide information about drug-drug interactions and about a low-dose colchicine regimen. *See* Takeda Br. 25-32. If Takeda is right, any subsequently approved Mitigare label would look different from the current one. The Mitigare label in turn is critical to the patent issues being litigated in Delaware: Whether Hikma's label "encourage[s], recommend[s], or promote[s] infringement" is probative of

Takeda's inducement claims. *Takeda Pharms.*, 785 F.3d at 631. A different label that more explicitly recites Takeda's patented uses could alter that calculus.

Reports of this case's demise thus have been greatly exaggerated.

II. HIKMA WAS REQUIRED TO REFERENCE COLCRYS.

Takeda's opening brief explained that (1) a 505(b)(2) applicant "relie[s] upon" another drug when that drug is necessary to the application's approval; and (2) the application for Mitigare relied on Colcrys. Takeda Br. 16-24. FDA contests both strands of this argument. But the statute compels the former conclusion, and the record compels the latter.

A. "Reliance" Means That A Drug Is Necessary To FDA's Approval.

FDA spends much of its energy disputing the common-sense proposition that a drug is "relied upon by the applicant for approval" under Section 505(b)(2) if it is necessary to FDA's approval—regardless of whether it is first invoked by the applicant or by FDA. To support its argument, FDA highlights at length the relationship between Hatch-Waxman's certification obligations and an applicant's reliance on another drug. FDA Br. 24-26. But everyone appears to agree that "reliance" is the trigger for an applicant's certification obligations. The pivotal question here is whether an applicant can avoid "reliance" on another drug by omitting mention of the drug and trusting FDA to fill in all the blanks. *See* Takeda Br. 19.

FDA argues (and the District Court held) that it is free to use proprietary data to support an approval without consequence because the statute discusses applicants only. Any other construction of the statute, it asserts, would be "untethered from the text." FDA Br. 26. What is more, it suggests Takeda "all but admits" as much. *Id.*

Takeda did nothing of the sort. As Takeda explained, the statute defines an applicant's certification duties, which apply whenever a previously approved drug is "relied upon by the applicant for approval of the application." Takeda Br. 16 (quoting 21 U.S.C. § 355(b)(2)). The statute focuses on "the applicant" because the applicant has the obligation to submit sufficient information to establish a drug's safety. *See* 21 U.S.C. § 355(d). In other words, the statute presumes that the agency is reviewing a complete data set, not a concept. If, rather than return an incomplete application, FDA opts to step into the applicant's shoes and pull additional necessary information on the applicant's behalf, it cannot escape the normal operation of Section 505(b)(2) by invoking the fiction that it acts outside the statutory scheme.

Congress's choice of the word "reliance" affirms as much. An applicant does not "rely" only on those drugs it references in the formal application submitted to FDA. If Congress had intended to create such a formalistic system, after all, the statute might require an applicant to certify only to those drugs that

the applicant "referenced" or "listed" or "submitted." *Reliance* is a more capacious concept. And used in this context, it indicates simply that a drug upon which an applicant "relies" is one that is necessary to FDA's approval of the application. *See, e.g.*, *Merriam Webster's Collegiate Dictionary* (11th ed.) (defining "rely" as "to be dependent"); *American Heritage Dictionary of the English Language* (5th ed.) (defining "rely" as "[t]o be dependent for support, help, or supply"). That interpretation makes good sense. FDA's alternative interpretation would elevate form over substance, converting the carefully crafted Hatch-Waxman Amendments into a minor paperwork requirement.

Enforcing the ordinary meaning of "reliance" would not "make a hash of the statute's operation," as FDA hyperbolically puts it. FDA Br. 28. The Hatch-Waxman "quid pro quo" remains in place between applicants (who receive the benefit of FDA's safety findings about the previously approved drug) and patent holders (who receive notice and may take action to enforce their patent rights). The sole statutory provision FDA believes is problematic, then, *see* FDA Br. 28, is a requirement that an applicant provide the necessary patent certification notice to the relied-upon drugs' patent holders within 20 days of filing the 505(b)(2) application. *See* 21 U.S.C. § 355(b)(3)(B)(i). But the very next provision of the statute, which the agency omits, provides another timeline under which additional certifications must be made "at the time at which the applicant submits [an]

amendment or supplement." *Id.* § 355(b)(3)(B)(ii). As Takeda has explained, an application that fails to reference a drug necessary to FDA's analysis should not be approved "until the deficiency is corrected"—presumably by amendment or supplement. Takeda Br. 19.[1] At the time of that amendment or supplement, the required patent certifications must be made. That is no "hash"; it is a simple application of the statutory text, which expressly contemplates that an applicant might not list all relied-upon drugs in its initial application.

Finally, FDA makes a brief stab at distinguishing some (but not all) of its past comments about reliance. First, it dismisses its repeated statement, preserved in the Federal Register, that an applicant "relies" on any studies "without which the application could not be approved." 54 Fed. Reg. 28872, 28890, 28891 (July 10, 1989). FDA now protests that those repeated statements are inapposite—apparently because the agency there was speaking in generalities about the 505(b)(2) process. FDA Br. 28-29. It is hard to see the relevance of that purported distinction; we are not discussing a case-specific policy here, either.

FDA also attempts to minimize its statement in a Citizen Petition Response that an applicant's certification obligations correspond to drug data "relied on by FDA for approval." JA649. The agency points out that the same Response

[1] Or, as FDA has indicated, it may require an applicant to submit a new 505(b)(2) application with a new reference, which would bring the application back within the 20-day subsection (i) time frame. *See* FDA Citizen Petition Response, Docket No. FDA-2008-P-0329 (Nov. 25, 2008), at 16 n.30.

mentions an applicant's reliance, too. FDA Br. 29. But that only underscores the point that an applicant necessarily "relies on" *any* drug necessary for approval of its application—even if FDA is the entity that introduces the drug's data into its assessment.

FDA flatly ignores the other authorities Takeda cited in its opening brief. It does not acknowledge that its own standard 505(b)(2) Assessment Form makes clear that an applicant relies on another drug if "the application cannot be approved without this reliance." JA834. Nor does the agency mention its concession below that "if FDA had relied" on another drug's study, it would have been obliged to reject a 505(b)(2) application as incomplete. JA338. The agency's silence speaks volumes.

It bears reiterating just what FDA is asking this Court to do. It is asking this Court to permit the agency to fill acknowledged gaps in a 505(b)(2) applicant's safety data, *see* FDA Br. 27, without any repercussions for the applicant's certification obligations. Under the agency's theory, a 505(b)(2) applicant could leave the "reference drug" line blank, FDA could fill in the blank and conduct a safety review relying on the drug it selects, and the applicant would not have "relied upon" that drug for approval. (This is not a far-fetched hypothetical; FDA actually, albeit accidentally, listed Colcrys as the referenced drug in this very case. *See* JA887.) According to FDA, so long as it wants an application approved and

does the applicant's work with a wink and a nod, the applicant can bypass the Hatch-Waxman requirements altogether. Such a system makes sense neither as a practical matter nor as a textual one.[2]

B. The Record Contradicts FDA's Assertion That It Did Not Rely On Colcrys.

As a fallback, FDA contends that even if Takeda's interpretation of the statute carries the day, the agency did *not*, in fact, rely on Colcrys data to approve Hikma's 505(b)(2) application. The administrative record shows otherwise, every couple of pages.

FDA does not dispute that [redacted]. But the agency and Hikma insist that FDA was never *relying* on Colcrys data when it talked about it; rather, it was "review[ing]," "compar[ing]," "offer[ing] recommendations" based on, "consider[ing]," "consult[ing]," and "assess[ing]" that data. FDA Br. 30-32; Hikma Br. 35.

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[2] FDA and Hikma both insist that a 505(b)(2) applicant need not reference the "most similar" approved drug. *See* FDA Br. 33; Hikma Br. 31. Takeda agrees. As Takeda's opening brief explained, FDA previously applied a "most similar" policy, but has since adopted a somewhat more flexible "most *appropriate*" standard. *See* Takeda Br. 19-20. The "most appropriate" standard, though, still must contain some objective content; otherwise, FDA could not instruct its reviewers to consider which drug "should be referenced," as it continues to do. JA835. And even if FDA were to entirely yield reference drug selection to applicants—thereby creating an "applicant's choice" standard—that new policy underscores the problem with its new "reliance" interpretation: A 505(b)(2) applicant may omit a *nearly identical* reference drug, but FDA may freely borrow from that obvious source of data.

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Whatever synonyms it uses, such pervasive "consulting" shows that Colcrys was critical to the approval of Mitigare. And it highlights how seriously FDA's approval in this case undermines the Hatch-Waxman protections for innovators. *See generally* Br. of Amicus Curiae Pharmaceutical Research and Manufacturers of America 23-26.

At least three specific examples further demonstrate that FDA's use of Colcrys data constituted flat-out borrowing. *See* Takeda Br. 21-24.

1. Mitigare package insert and medication guide. In its packaging and labeling review, [redacted] nevertheless does not amount to real "reliance" for purposes of determining Mitigare's safety. *See* FDA Br. 31. Its own regulations, however, demonstrate that a drug's labeling is an integral part of the ultimate safety determination. *See* 21 C.F.R. § 201.56(a)(1) ("The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug."). [redacted]

[redacted]

In its brief, FDA downplays its labeling decisions because they came from the Office of Prescription Drug Promotion, rather than the Review Division itself. *See* FDA Br. 31. Of course, FDA does not contend that the Review Division considered Colcrys irrelevant [redacted] So even if the agency could somehow insulate itself by delegating to certain internal sub-groups the prerogative to "rely" on an unreferenced pioneer's data (which makes little sense anyway), the agency's reliance on Colcrys was widespread and recurring.

2. Results of drug-drug interaction studies. FDA's analysis of Colcrys's drug-drug interaction studies was integral to its approval of Mitigare. In order to determine the risks of administering colchicine with other drugs, [redacted] *See id.* FDA concedes that Colcrys data was used "to determine the proper regulatory approach" to Hikma's 505(b)(2) application. FDA

[3] Mutual is Takeda's predecessor.

Br. 32; *see* JA894. As its brief acknowledges, FDA used both sets of data because one set of drug-drug interaction studies "actually did not contradict" the other. FDA Br. 32 (quoting JA33). The consideration of both studies in tandem to assess the safe use of colchicine is a quintessential example of the agency's reliance on Colcrys data.[4]

FDA now claims that it was merely *comparing* two data sets—apparently out of idle curiosity—and that Colcrys data was thus irrelevant to its approval of Mitigare. FDA Br. 32-33. For that, it cites a record statement [redacted] JA780. But FDA's say-so does not make it so. This Court has long recognized that it may not "sanction agency action when the agency merely offers conclusory and unsupported postulations in defense of its decisions or when it ignores contradictory evidence in the record." *Prof'l Pilots Fed'n v. FAA*, 118 F.3d 758, 771 (D.C. Cir. 1997). That is all FDA offers here: In the face of [redacted]

[4] Both FDA and Hikma repeatedly invoke colchicine's long history, presumably in an attempt to minimize the importance of Mutual's studies. They conveniently overlook how turbulent that history was. Before it pulled colchicine from the market in 2007, FDA received over *seven hundred* reports of adverse events associated with colchicine toxicity, including 169 deaths. *See* 75 Fed. Reg. 60768, 60769 (Oct. 1, 2010). It was against that background that FDA later approved Colcrys. And when it did, the agency issued a Safety Alert publicizing the "previously uncharacterized safety concerns" Mutual's new data had quantified, along with the "important safety considerations found in the approved prescribing information" for Colcrys. JA126. FDA also stated without reservation that "the requirements for approval of a single-ingredient colchicine product have changed" because of Mutual's groundbreaking studies. JA683.

[redacted], FDA cannot credibly claim that Colcrys was beside the point.

3. Drug-drug interaction warnings on the Mitigare label. Finally, the Mitigare label itself cautions against the co-administration of colchicine with P-gp and CYP3A4 inhibitors because those inhibitors may cause "significant increases in systemic colchicine levels." JA699. The approved label thus piggybacks on *Mutual's* studies, not Hikma's. Hikma, after all, conducted four drug-drug interaction studies that showed *no* effects from the co-administration of colchicine with various inhibitors. *See* JA701. Indeed, in its review of the proposed Mitigare label, FDA noted that any warnings about co-administration [redacted] JA881. Aside from raising the possibility of drug-drug interactions, the Mitigare label—like the Colcrys one—recommends that a "reduced daily dose should be considered." JA699. The lack of specificity in the Mitigare dose adjustments is problematic for other reasons. *See infra* at 17-20. But the concept of responding to certain drug-drug interactions with dose reductions finds its source *only* in the Colcrys label.

FDA responds that colchicine's drug-drug interaction potential was known in the literature before Mutual's studies. FDA Br. 31-32. That may be true, but, as FDA itself has pointed out, [redacted]

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[redacted] JA712. Beyond that, Mutual's studies led to specific dose reductions, whereas the prior literature had simply recommended "avoidance when possible and caution when necessary." JA776. The combination of the Mitigare label's reference to quantitative studies ("significant increases in systemic colchicine levels") and its recommendation of dose adjustments ("reduced daily dose") goes well beyond the background literature's vague cautionary language. The Mitigare label instead repurposes the Colcrys label and the proprietary studies supporting it.[5]

III. FDA FAILS TO PROVIDE A REASONED EXPLANATION FOR ITS DUAL DEPARTURE FROM AGENCY PRECEDENT.

FDA did not only deviate from the Hatch-Waxman scheme in approving Hikma's Mitigare application; it departed from its own precedent. *See* Takeda Br. 25-33. In its responsive brief, FDA now suggests that precedent never existed. *See* FDA Br. 39. Its skepticism is unwarranted. In responding to Mutual's Citizen Petition, FDA repeatedly and categorically described the safe labeling necessary for all single-ingredient colchicine products. *See, e.g.*, JA670 ("labeling for any single-ingredient oral colchicine product needs to include adequate information on drug-drug interactions, including relevant dose adjustments needed to prevent

[5] Hikma's insistence that "Takeda points to nothing in the Mitigare® label that comes from Colcrys® data," Hikma Br. 36, is thus inaccurate, as is Hikma's inexplicable statement that the co-administration warnings on the Mitigare label "are consistent with both companies' studies." Hikma Br. 39.

unnecessary toxicity"); *id.* ("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").

Of course, an agency is permitted to *change* its policies—with a reasoned explanation. *See Friedman v. Sebelius*, 686 F.3d 813, 828 (D.C. Cir. 2012). But the record contradicts FDA's assertion that there *were never any* policies.

For similar reasons, the agency's claim that its scientific determinations are entitled to deference, *see* FDA Br. 43 and Hikma Br. 43, is irrelevant. Takeda is not challenging FDA's scientific judgments. It is challenging the agency's unreasoned shift in how it *applies* those judgments. Even if a new policy is permissible, an agency may not "depart from a prior policy *sub silentio* or simply disregard rules that are still on the books." *FCC v. Fox Television Stations*, 556 U.S. 502, 515 (2009). In approving Mitigare, FDA did just that. Twice.

A. The Record Does Not Justify The Omission Of Drug-Specific Dose Adjustments.

Takeda explained in its opening brief that the Mitigare label violates FDA safety standards because it includes generic warnings about drug-drug interactions rather than specific dose adjustments. Takeda Br. 25-28. In response, FDA doubles down on the same partial explanation found in the administrative record: *Some* drugs on the Colcrys label might not interact with colchicine. Hikma's

studies showed that certain drugs can be administered without a dose adjustment, and its label states that those results "should not be extrapolated to other co-administered drugs." JA701; *see* FDA Br. 40. From this, FDA asserts that there is [redacted]

Takeda has never contested that scientific judgment, or FDA's basis for adopting it. The problem is that FDA's proffered explanation—[redacted]—does not actually explain why FDA allowed Hikma to *omit* the specific inhibitors that Mutual tested, which *do* cause harmful interactions with colchicine. As to those, Mutual's drug-drug interaction studies indicated that certain common drugs like clarithromycin, which has been associated with numerous deaths when co-administered with colchicine, increase colchicine blood levels by more than 200%. *See* JA898 [redacted]; JA146 (table of colchicine blood level increases). FDA does not (and cannot) contest this. Nor does it contest that

it previously determined that specific dose recommendations were necessary to colchicine's safe use. *See* JA686-687 ("product labeling for any single-ingredient oral colchicine product *needs to include* . . . relevant dose adjustments") (emphasis added). Nor does it contest that Mutual chose inhibitors with reported adverse effects, [redacted] JA779. Obfuscation aside, then, the question remains: Why do specific dosing recommendations for the handful of critical drugs Mutual studied no longer "help mitigate th[e] risk" of "severe drug interactions"? JA686.

[redacted]

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[redacted] JA935. In short, FDA fails to justify the omission of all dose adjustments.

At the end of its analysis, FDA tacks on an argument [redacted] JA713. And more to the point, it contradicts FDA's prior conclusion that "labeling for *any* single-ingredient oral colchicine product" needs to include information on relevant dose adjustments necessary "to prevent unnecessary toxicity." JA670 (emphasis added). Its categorical language was not inadvertent. FDA explained in the same Citizen Petition Response that "it has been increasingly recognized that these drug interactions can result in serious colchicine toxicity in patients who are on 'standard' daily low-dose prophylactic regimens." JA686. That is why the agency chose to require dose adjustments on the label for "any single-ingredient oral colchicine product," not just for colchicine products indicated for acute flares. JA686-687. The agency's about-face now is both unsupported and disturbing.

B. The Record Does Not Support Restricting The Low-Dose Regimen To Colchicine Products Indicated For Acute Flares.

Before it approved Mitigare, FDA required that "the labeling for a single-ingredient colchicine product seeking approval for prophylaxis of gout flares must inform healthcare providers" about the low-dose regimen developed in Mutual's AGREE trial. JA670; *see* Takeda Br. 29-32. And yet the Mitigare label omits any mention of it.

FDA first attempts to distinguish its prior policy by arguing that it applied only to duplicates of Colcrys—which Mitigare technically is not, because it is a capsule instead of a tablet. *See* FDA Br. 44-45. But FDA's statement in its Citizen Petition Response was not so limited. To be sure, one of the questions Mutual raised involved whether Hikma had impermissibly sought approval of a duplicate through a 505(b)(2) petition rather than an ANDA. JA668. Mutual's question about appropriate labeling, however, applied to *all* single-ingredient oral colchicine products. *See id.* FDA's answer was equally broad; it covered "single-ingredient colchicine product[s]," JA670, not "single-ingredient 0.6 mg colchicine tablets." And FDA offers no reason why the difference in form of administration would undercut its safety conclusions.

FDA's alternative explanation is that, because Mitigare was approved only for prophylaxis, it was reasonable to omit information about a low-dose regimen aimed at treating acute flares. *See* FDA Br. 45-46. The agency cites the same

single record statement on which the District Court relied, *see* JA773, without confronting any of the problems Takeda pointed out in its opening brief, *see* Takeda Br. 31-32.[6] Most critical among those is the agency's failure to acknowledge its prior analysis on the same subject. FDA previously concluded that [redacted] *See* JA691, 946, 1007. If FDA no longer thought that to be the case when it approved Mitigare, the APA required it to explain why. *See Lone Mtn. Processing, Inc. v. Sec'y of Labor*, 709 F.3d 1161, 1164 (D.C. Cir. 2013).

Hikma protests that the reasons for FDA's new policy need not be better than the reasons for the old one. *See* Hikma Br. 46 (citing *Fox Television*, 556 U.S. at 515). True—but irrelevant. A reasoned explanation requires, at a minimum, that an agency "display awareness that it *is* changing position." *Fox Television*, 556 U.S. at 515. In approving Mitigare, FDA twice failed that basic APA requirement.

[6] Hikma, for its part, cites *its submissions* to FDA regarding the supposed limitations of the AGREE trial. *See* Hikma Br. 44-45. Given that FDA did not adopt Hikma's rationale, the company's submissions are irrelevant.

CONCLUSION

For the foregoing reasons, and those in Takeda's opening brief, the District Court's decision should be reversed and the case remanded with instructions to enter an order granting Takeda's motion for summary judgment.

Dated: October 30, 2015

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. P. 32(a)(7)(C), I hereby certify that this Reply Brief for Appellant complies with the type-volume limitation of this Court's July 1, 2015 Order because the brief contains 4,944 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii) and Circuit Rule 32(e)(1).

I further certify that this brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because the brief has been has been prepared in Times New Roman 14-point font using Microsoft Word 2010.

/s/ Catherine E. Stetson
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CERTIFICATE OF SERVICE

I hereby certify that on October 30, 2015, the foregoing public Reply Brief for Appellant was electronically filed through this Court's CM/ECF system, which will send a notice of filing to all registered users.

/s/ Catherine E. Stetson
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