IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

TAKEDA PHARMACEUTICALS U.S.A., INC.

Plaintiff,

v.

SYLVIA MATHEWS BURWELL, in her official capacity as SECRETARY, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES,

and

MARGARET HAMBURG, M.D., in her official capacity as COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION

Defendants,

and

HIKMA PHARMACEUTICALS PLC AND WEST-WARD PHARMACEUTICAL CORP.,

Intervenor-Defendants.

C.A. No. 1:14-cv-01668-(KBJ)

HIKMA PHARMACEUTICALS PLC AND WEST-WARD PHARMACEUTICAL CORP.'S SUPPLEMENTAL BRIEF IN OPPOSITION TO PERMANENT INJUNCTION

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INTRODUCTION

In response to this Court's order of November 5, 2014, Intervenors Hikma Pharmaceuticals PLC and West-Ward Pharmaceutical Corp. (together, "Hikma") submit this supplemental brief opposing Takeda's request for a permanent injunction. As the administrative record shows, FDA approved Hikma's drug branded as Mitigare™—a colchicine product indicated for prophylaxis of gout flares—after carefully determining that it is both safe and effective. The approved label includes warnings designed to ensure that doctors and patients use the product safely.

Both the colchicine compound and the use of the drug as a prophylaxis are ancient, and thus neither is patented. In light of this, FDA correctly determined that Hikma had no obligation to rely upon Takeda's colchicine product, Colcrys®, nor to certify to its patents under the Hatch-Waxman Act. That is precisely how Congress designed Hatch-Waxman to work. And by granting its well-reasoned approval of generic colchicine, FDA did precisely what Congress tasked it to do.

Takeda asks this Court to second-guess FDA's safety determinations and rescind a new drug approval via a mandatory injunction. This is an extraordinary and, as far as we can tell, unprecedented request. It is also completely meritless. FDA carefully considered the safety issues raised by Takeda, specifically in view of its 2011 ruling in response to Takeda's citizen petition. *E.g.*, AR 88-106, 667-72.[1] Moreover, FDA complied with the letter and spirit of the Hatch-Waxman Act and its own implementing regulations when it approved Hikma's application through the 505(b)(2) pathway without reliance on any of Takeda's data. *Id.* Both of those determinations are subject to a generous amount of deference.

[1] "AR ___" refers to the excerpted administrative record from FDA attached as Exhibit B to Takeda's reply in support of its motion for temporary restraining order or preliminary injunction (D.I. 21).

Takeda has fallen far short of proving entitlement to any form of relief. Hikma has no desire to burden the Court with duplicative briefing. Thus, it relies principally on its prior briefing and argument, supplementing the record here by briefly recapping why Takeda's request for declaratory and permanent injunctive relief should be denied and responding to Takeda's new arguments raised in its reply and at the previous hearing.

ARGUMENT

I. TAKEDA HAS FAILED TO DEMONSTRATE THAT THE MITIGARE™ LABEL IS UNSAFE.

A. FDA's Labeling Decisions Are Entitled To Considerable Deference, Particularly Because FDA Expressly Addressed Takeda's Safety Concerns.

Takeda asks this Court to hold that FDA acted arbitrarily and capriciously in deeming Mitigare™ safe—a decision falling squarely within the realm of expert decision-making delegated to FDA by Congress. *See* 5 U.S.C. § 706(2)(A). The onerous burden that Takeda faces cannot be overstated. The arbitrary-and-capricious standard is "narrow and highly deferential" and "presumes agency action to be valid." *ViroPharma, Inc. v. Hamburg*, 898 F. Supp. 2d 1, 16-17 (D.D.C. 2012). Where, as here, the plaintiff asks to set aside "[a] scientific determination," the Court "must generally be at its most deferential." *Baltimore Gas & Elec. Co. v. NRDC*, 462 U.S. 87, 103 (1983). 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." *Am. Paper Inst. v. EPA*, 660 F.2d 954, 963 (4th Cir. 1981) (citing and quoting *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976) (en banc)).

This burden is compounded by the fact that FDA considered the very safety concerns of which Takeda now complains. When approving Mitigare™, FDA was well aware of its 2011 response to Takeda's citizen petition and explained its approval decision in light of that ruling.

For example, FDA directly addressed Takeda's safety concerns regarding acute gout flares, noting that, "[a]lthough the applicant [Hikma] is not seeking an indication for the treatment of acute gout flares," the Mitigare™ label would "include a Limitations of Use statement that the safety and effectiveness of Mitigare for acute treatment of gout flares during prophylaxis has not been studied"—thus alerting healthcare providers that "*Mitigare should not be used in this way*." AR 113 (emphasis added). This was a well-reasoned step taken to address the unique safety issues of this case.

FDA also considered Takeda's safety concerns regarding drug-drug interactions ("DDIs"). The agency explained that, "in 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 [the] detailed dose modification recommendations" in the Colcrys® label. AR 672 (emphasis added). FDA further considered the effect of having "different labeling for the two single-ingredient oral colchicine products [*i.e.*, Colcrys® and Mitigare™]" and "did not believe this was a major issue." AR 670, 672.

Thus, this is not a case where the agency overlooked a crucial argument, did not consider key evidence, or "failed to provide a reasoned explanation for its decision." *See, e.g.*, *Sw. Power Pool, Inc. v. FERC*, 736 F.3d 994, 995 (D.C. Cir. 2013). Here, FDA addressed the very concerns raised by Takeda in this suit. That distinction places this case squarely in the category of APA claims that are routinely rejected: those where the "arbitrary-and-capricious challenge boils down to a policy disagreement with [the agency]," but where the agency's decision "is both supported by the record and rationally explained." *See, e.g.*, *Pub. Citizen, Inc. v. NHTSA*, 374 F.3d 1251, 1263 (D.C. Cir. 2004).

B. Takeda Has Failed To Show That Mitigare™ Is Unsafe For Acute Gout Flares.

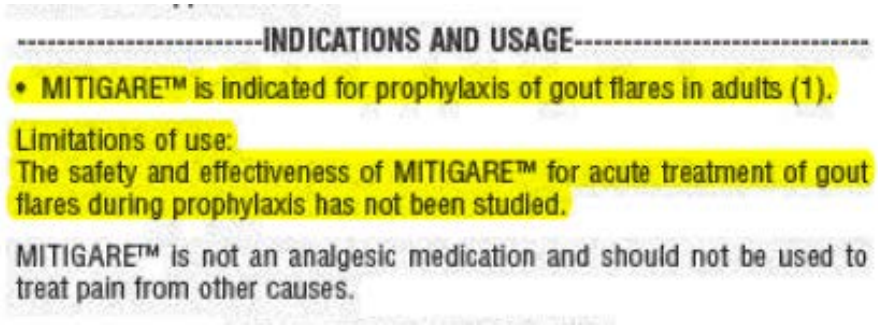
Takeda cannot seriously contend that FDA failed to consider a major safety issue. Rather, Takeda's real request is for this Court to second-guess FDA's conclusions and find Hikma's label unsafe. But, again, the Court "must generally be at its most deferential" when reviewing these scientific judgments. *Baltimore Gas & Elec. Co*., 462 U.S. 87, 103 (1983). The administrative record amply supports FDA's safety determination and, thus, Takeda's meritless argument should be rejected.

It is telling that Takeda does not dispute that Mitigare™ is safe for its only indicated use—prophylaxis of gout flares. Instead, according to Takeda, the Mitigare™ label is "not safe" because it does not include the "low-dose regimen" for the acute gout flare indication of Colcrys®. Reply Br. 8, D.I. 21. As Hikma has already explained, this argument is both legally and factually meritless. *See* Opposition Br. 21-23, D.I. 16.

First, Takeda has cited no precedent to support rescinding FDA approval for a new drug on the ground that it is unsafe for an off-label use. This is not surprising. "FDA does not grant across-the-board approval to market a drug. Rather, it grants approval to make, use, and sell a drug for a specific purpose for which that drug has been demonstrated to be safe and efficacious." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1356 (Fed. Cir. 2003). Accordingly, Takeda's arguments (baseless as they are) regarding the safety of Mitigare™ for the off-label treatment of acute flares are legally irrelevant. The question before this Court is whether FDA arbitrarily approved Mitigare™ *for its indicated use*. *See Hospira, Inc. v. Burwell*, 2014 WL 4406901, at *17 (D. Md. 2014) ("FDA is not obligated to consider how the product might be used by physicians beyond the approved labeling."). Takeda has nothing to say on that matter.

Takeda's reliance on 21 C.F.R. § 201.57(c)(6) does not change this result. According to Takeda, this regulation required FDA to include in Hikma's label the Colcrys® dosage warnings because treatment of acute gout flares is a "common off-label use." Reply Br. 4, D.I. 21; *see also* Motion Hr'g Tr. 26:8-19, Nov. 4, 2014. But § 201.57(c)(6) merely gives FDA broad discretion to decide, in limited circumstances, whether (and what) information to include in a drug label about an off-label use: "A specific warning relating to a use not provided for under the 'Indications and Usage' section ***may*** *be required by FDA* . . . if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard." (Emphasis added.)

Here, even assuming that Mitigare™ could be "commonly prescribed" for acute gout flares, FDA *did* include "[a] specific warning" in the Mitigare™ label related to the use of Hikma's product for acute flares, making it clear that FDA has not approved that use:



----------INDICATIONS AND USAGE----------

• MITIGARE™ is indicated for prophylaxis of gout flares in adults (1).

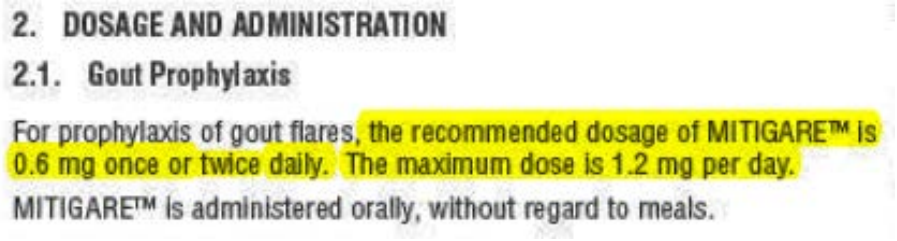
Limitations of use:
The safety and effectiveness of MITIGARE™ for acute treatment of gout flares during prophylaxis has not been studied.

MITIGARE™ is not an analgesic medication and should not be used to treat pain from other causes.

Wong Decl., D.I. 16-9, Ex. B (Mitigare™ Label). Far from being coy, FDA included this express limitation to inform providers that "Mitigare should *not* be used in this way." AR 113 (emphasis added).

Furthermore, the notion that any doctor will prescribe Mitigare™ off-label to treat acute gout flares at doses sufficient to cause an overdose is far-fetched, to say the least. As discussed at the last hearing (Motion Hr'g Tr. 55:20-56:1, Nov. 4, 2014), the maximum *daily* dosage of

Mitigare™ approved by FDA is 1.2 mg per day—far less than the 1.8 mg *hourly* dosage approved for Colcrys®:



2. DOSAGE AND ADMINISTRATION

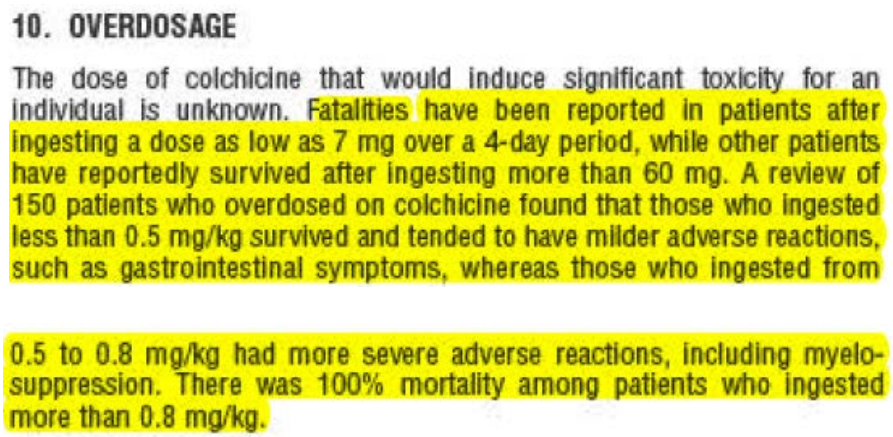
2.1. Gout Prophylaxis

For prophylaxis of gout flares, the recommended dosage of MITIGARE™ is 0.6 mg once or twice daily. The maximum dose is 1.2 mg per day.

MITIGARE™ is administered orally, without regard to meals.

Compare Wong Decl., D.I. 16-9, Ex. B (Mitigare™ Label), *with id.*, Ex. S (Colcrys® label).

Also, as Judge Robinson found in the related patent case in Delaware, Takeda has "not demonstrated" that Hikma's label even encourages doctors to "follow the [admittedly safe] patented method of use for treatment of the acute gout flare," D. Del. Mem. Op., D.I. 38-1 at 8-10, much less that doctors would use Hikma's product for that method at dosing considered unsafe. This is particularly true given that the Mitigare™ label contains specific warnings regarding potential toxicity from an overdose:



10. OVERDOSAGE

The dose of colchicine that would induce significant toxicity for an individual is unknown. Fatalities have been reported in patients after ingesting a dose as low as 7 mg over a 4-day period, while other patients have reportedly survived after ingesting more than 60 mg. A review of 150 patients who overdosed on colchicine found that those who ingested less than 0.5 mg/kg survived and tended to have milder adverse reactions, such as gastrointestinal symptoms, whereas those who ingested from

0.5 to 0.8 mg/kg had more severe adverse reactions, including myelosuppression. There was 100% mortality among patients who ingested more than 0.8 mg/kg.

Wong Decl., D.I. 16-9, Ex. B (Mitigare™ Label).

Given the express limitations and warnings in Hikma's label that directly address each of Takeda's concerns here, FDA appropriately concluded that Mitigare™ is safe for its indicated use and presents no safety concern for potential off-label use to treat acute gout flares. In FDA's

own words, it "did not believe this was a major issue." AR 672. That conclusion is entitled to the "most deferen[ce]" an agency determination can receive. *Baltimore Gas & Elec.*, 462 U.S. at 103.

C. Takeda Has Failed To Show That Mitigare™ Is Unsafe For Certain Drug-Drug Interactions.

Takeda next asserts that Mitigare™ is unsafe because it does not include "dose adjustment recommendations for certain [DDIs]" contained in the Colcrys® label. Reply Br. 4, D.I. 21. In support, Takeda cites FDA's 2011 citizen petition ruling—which, as discussed, FDA expressly considered when approving Hikma's product. *E.g.*, AR 88-106, 667-72. Once again, Takeda's argument runs headlong into agency deference.

FDA rejected Takeda's citizen petition argument that 505(b)(2) applicants, as opposed to ANDA applicants, had to copy the DDI data in Colcrys®'s label. Instead, it ruled only 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." Wong Decl., D.I. 16-9, Ex. A at 19-20 (emphasis added). FDA "decline[d] to speculate" on the specific DDI and dosage information that would be necessary for 505(b)(2) applicants. *Id.* at 21. As it explained, "in light of the significant amount of non-product-specific published scientific literature . . . and additional non-product-specific literature that may become available over time," 505(b)(2) applicants may well be able to submit "adequate safety and effectiveness data to support approval without reference to Colcrys." *Id.* at 21.

That is precisely what happened here. The safety data Hikma submitted to support its Mitigare™ label, including new studies, demonstrated why the *general* warning, in addition to instructions to monitor the individual patient, in Hikma's label is not only safe, but potentially

even preferable to the *specific*, one-size-fits-all dose reductions in the Colcrys® label. As FDA explained, the results of Hikma's independent testing were "unexpected" (AR 96), because the co-administration of Mitigare™ with the tested drugs did not result in the same type of colchicine toxicity observed in Takeda's testing. AR 96-98; *see also* AR 667-72 (memorandum entitled "The Curious Case of Colchicine: What to Do About Conflicting Drug Interaction Study Results for the Same Molecular Entity").

FDA "carefully considered possible explanations" for these new findings, including the possibility that that CYP3A4 and P-gp inhibitors studied by Hikma behaved differently than those studied by Takeda and in previous literatures. AR 96-97. While FDA observed differences in these studies, "the clinical pharmacology team concluded that the data from [Hikma's] studies were interpretable and conformed to the recommendations in the draft Guidance for Industry." AR 97. It further found that Hikma's DDI studies "raise[d] important new questions about the sensitivity of colchicine": specifically, they suggested that "it may not be appropriate to extrapolate drug interaction potential (and thus dose modification recommendations) from one CYP3A4 inhibitor to another, or one P-gp inhibitor to another, as individual drugs may have different overall interaction potential with colchicine depending on the degree to which they interact with multiple pathways." AR 97.

"Based on" the new information presented by Hikma, FDA concluded that "*general cautionary language* informing patients about DDI potential of colchicine will be included in [the Mitigare™] label." AR 49 (emphasis added). FDA specifically decided to "forego detailed dose modification recommendations"—such as those in the Colcrys® label—and instead to "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." AR 672. This finding reflects FDA's scientific judgment that "[Hikma] provided adequate clinical pharmacology information to support their 505(b)(2) NDA for 0.6 mg Colchicine Capsules." AR 49. That judgment is imminently reasonable and, again, is entitled to the "most deferen[ce]." *Baltimore Gas & Elec.*, 462 U.S. at 103.

Unable to contest this evidence, Takeda has tried to recast FDA's approval of Mitigare™ as "revert[ing] back to the old, pre-Colcrys® [labeling] regime that had resulted in unnecessary toxicity and deaths." Reply Br. 10, D.I. 21. As discussed at the hearing (Motion Hr'g Tr. 62:24-63:13, Nov. 4, 2014), however, the administrative record does not support this argument. Indeed, Hikma's old colchicine product (withdrawn in 2010) contained no DDI warning. Instead, its 2003 colchicine label contained the following dosing information that made no mention of CYP3A4 or P-gp inhibitors:

DOSAGE AND ADMINISTRATION: Colchicine should be started at the first warning of an acute attack; a delay of a few hours impairs its effectiveness. The usual adult dose is 1 or 2 tablets initially, followed by 1 tablet every one to two hours until pain is relieved or nausea, vomiting, or diarrhea develops. Some physicians use 2 tablets every two hours. Since the number of doses required may range from six to 16, the total dose is variable. As interval treatment, 1 tablet may be taken one to four times a week for the mild or moderate case, once or twice daily for the severe case.

INDICATIONS AND USAGE: Colchicine is indicated for the treatment of gout. It is effective in relieving the pain of acute attacks, especially if therapy is begun early in the attack and in adequate dosage. Many therapists use colchicine as interval therapy to prevent acute attacks of gout. It has no effect on nongouty arthritis or on uric acid metabolism.

CONTRAINDICATIONS: Colchicine is contraindicated in patients with gout who also have serious gastrointestinal, renal, or cardiac disorders.

WARNINGS: Colchicine can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking it, the woman should be apprised of the potential hazard to the fetus.

PRECAUTIONS: General Precautions: Colchicine should be administered with great caution to aged and debilitated patients, especially those with renal, gastrointestinal, or heart disease. Reduction in dosage is indicated if weakness, anorexia, nausea, vomiting, or diarrhea appears.

Wong Supp. Decl., Ex. A. Hikma's 2008 colchicine label was likewise silent on the issue of adverse interaction with CYP3A4 and P-gp inhibitors:

DOSAGE AND ADMINISTRATION: Colchicine tablets are administered orally.

For Acute Gouty Arthritis – The usual dose to relieve or abort an attack is 0.6 mg (one tablet) to 1.2 mg (2 tablets). This dose may be followed by one tablet every hour or two tablets every two hours, until pain is relieved or until diarrhea ensues. Each patient should learn the dose he/she needs and keep the medication at hand for use at the first sign of an attack. After the initial dose, it is sometimes sufficient to take one tablet every two or three hours. The drug should be stopped if there is gastrointestinal discomfort or diarrhea. (Opiates may be needed to control diarrhea). In subsequent attacks, the patient should be able to judge his/her medication requirement accurately enough to stop short of his/her "diarrheal dose." The total amount of colchicine needed to control pain and inflammation during an attack usually ranges from 4 mg to 8 mg. Articular pain and swelling typically abate within 12 hours and are usually gone in 24 to 48 hours. An interval of three days between colchicine courses is advised in order to minimize the possibility of cumulative toxicity.

CONTRAINDICATIONS: Colchicine is contraindicated in patients with a known hypersensitivity to the drug, in those with serious gastrointestinal, renal, hepatic, or cardiac disorders, and in those with blood dyscrasias.

WARNINGS: Colchicine arrests cell division in animals and plants. It has adversely affected spermatogenesis in humans and in some animal species under certain conditions.

PRECAUTIONS: General: Colchicine should be administered with caution to aged or debilitated patients, and to those with early manifestations of gastrointestinal, renal, hepatic, cardiac or hematological disorders (See **CONTRAINDICATIONS**).

If nausea, vomiting or diarrhea occurs, the drug should be discontinued.

Wong Supp. Decl., Ex. A. This label made clear that colchicine use should be "stopped" at the onset of gastrointestinal discomfort. But that is a far cry from the DDI information included in the Mitigare™ label.

In fact, the differences as to safety information between Hikma's old and new product labels could not be more pronounced. Hikma's label for Mitigare™ contains express warnings against co-administration of Mitigare™ with any CYP3A4 or P-gp inhibiting drugs. As the label makes clear four times, concomitant use of these drugs with Mitigare™ should be "avoided":

----------DRUG INTERACTIONS----------

- Co-administration of P-gp or CYP3A4 inhibitors or inhibitors of both P-gp and CYP3A4 (e.g., clarithromycin or cyclosporine) have been reported to lead to colchicine toxicity. The potential for drug- drug interactions must be considered prior to and during therapy.
- Concomitant use of MITIGARE™ and inhibitors of CYP3A4 or P-gp should be avoided if possible. If co-administration of MITIGARE™ and an inhibitor of CYP3A4 or P-gp is necessary, the dose of MITIGARE™ should be reduced and the patient should be monitored carefully for colchicine toxicity (7, 12.3).

Wong Decl., D.I. 16-9, Ex. B (Mitigare™ Label).

Nothing in the administrative record—or, for that matter, outside it—supports Takeda's speculation that any doctor will ignore the avoidance warning and even find it "necessary" to co-administer Mitigare™ with any CYP3A4 or P-gp inhibiting drugs. *See* Motion Hr'g Tr. 57:23-

58:5, Nov. 4, 2014 (noting that providers commonly prescribe NSAIDs to treat acute gout flares). To be sure, it is not patient safety that is driving Takeda's lawsuit—it is the prospect of losing a monopoly.

II. THERE IS NO BASIS TO SECOND-GUESS FDA'S INTERPRETATION OF THE HATCH-WAXMAN ACT, UNDER WHICH HIKMA HAD NO OBLIGATION TO RELY ON COLCRYS® OR CERTIFY TO TAKEDA'S PATENTS.

Takeda alternatively argues that FDA should have rejected Hikma's 505(b)(2) application because it relies upon Col-Probenecid® instead of Colcrys®. It cites no statutory text to support this bald claim. That, of course, is because the Hatch-Waxman Act does not contain any restraint on a sponsor's selection of listed drugs to rely upon in a 505(b)(2) application. Congress's silence was intentional.

But even if the statute were ambiguous, Takeda would have to overcome *Chevron* deference. As the D.C. Circuit has made clear, "[i]n a suit challenging agency action, it is not for the court to choose between competing meanings of an ambiguous statute when the agency charged with its administration has not weighed in first." *Teva Pharm. USA, Inc. v. FDA*, 441 F.3d 1, 4 (D.C. Cir. 2006) (internal quotation marks omitted). Instead, "[w]hen a statute is ambiguous, Congress has left a gap for the agency to fill." *Id.* (citing *Chevron USA Inc. v. Natural Res. Def. Council*, 467 U.S. 837, 843-44 (1984)). In that circumstance, a "court's interpretation prevails only if it 'follows from the unambiguous terms of the statute and thus leaves no room for agency discretion.'" *Id.* (citation omitted). Here, FDA has expressly (and concededly) interpreted § 502(b)(2) to place no constraint on a sponsor's ability to rely upon a listed drug of its choice to support a new drug application, so long as that choice is scientifically justified. It is beyond dispute that Col-Probenecid® is an appropriate drug upon which Hikma could have relied, particularly given that Takeda relied upon the *same drug* to support its 505(b)(2) application for Colcrys®.

The applicable statutory text is straightforward: Section 505(b)(2) permits an applicant, such as Hikma, to "rel[y] upon" safety and efficacy data previously submitted to FDA for the "drug" (here, colchicine), even if the pertinent testing "were not conducted by or for the applicant" or "the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." 21 U.S.C. § 355(b)(2). The statute requires the applicant to provide a patent certification, but only "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*." *Id.* § 355(b)(2)(A) (emphasis added).

FDA has construed this statute by promulgating regulations and publishing "Guidance for Industry," which Takeda has referenced in its papers. *See* Compl., D.I. 1-1, Ex. 11 ("Guidance"). According to this Guidance, 505(b)(2) applicants may rely on "published literature" and/or FDA's prior "finding of safety and effectiveness for an approved drug." *Id.* at 2. As FDA explained, this process allows 505(b)(2) applicants to rely on data previously submitted for an earlier approved drug (referred to as a "listed drug"), thus avoiding a need to conduct "duplicative studies":

> This mechanism, which is embodied in a regulation at 21 CFR 314.54, essentially makes the Agency's conclusions that would support the approval of [an Abbreviated New Drug Application for a 'duplicate' generic product] available to an applicant who develops a modification of a drug. . . . This approach is intended to encourage innovation in drug development *without requiring duplicative studies to demonstrate what is already known about a drug* while protecting the patent and exclusivity rights for the approved drug.

Id. at 2-3 (emphasis added); *see* 21 C.F.R. § 314.54(a)(1)(iii).

The regulation cited in this guidance confirms that a 505(b)(2) application "need contain only that information needed to support the modification(s) of the listed drug." *Id.* § 314.54(a). Thus, as Takeda pointed out in its reply brief, it is the "*sponsor* interested in submitting a 505(b)(2) application"—here, Hikma—that "*should determine* which listed drug(s) is most

appropriate for its development program" Reply Br. 3, D.I. 21, Ex. C. (emphasis added) ("Reckitt Citizen Pet. Resp."). FDA will respect the sponsor's selection of a listed drug so long as it is "scientifically appropriate." Wong Supp. Decl., Ex. B at 12 ("Pfizer Citizen Pet. Resp."). As FDA emphasizes, "§ 314.54 makes clear that FDA interprets section 505(b)(2) to permit approval of an application that relies on the finding of safety and effectiveness of a listed drug to the extent such reliance is *scientifically justified*." *Id.* (emphasis added).

FDA's Guidance further explains that "[a]pproval or filing of a 505(b)(2) application . . . may be delayed because of patent . . . rights *that apply to the listed drug*." Guidance at 7 (citing "21 CFR. 314.50(i), 314.107, and 314.108 and section 505A of the Act"). The 505(b)(2) applicant must submit a "patent certification"—but, again, only "with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that *claim a use for the listed or other drug*[.]" Guidance at 8 (emphasis added) (citing "21 C.F.R. 314.54(a)(1)(vi)").

A 505(b)(2) applicant thus is not required to certify to any patents where, as here, the drug on which the applicant relies is not associated with any patents. This interpretation of the statute and regulations makes sense because, as the Supreme Court explained, FDA's position is that it "lacks both [the] expertise and [the] authority' to review patent claims" and thus views "its own role with respect to patent listing [a]s ministerial." *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1677 (2012) (first and second alterations in original) (internal quotation marks omitted).

Takeda does not challenge FDA's interpretation of § 505(b)(2), or its ministerial role in addressing patent issues. Nor could it: "In a suit challenging agency action, it is not for the court

to choose between competing meanings of an ambiguous statute . . . ." *Teva Pharm. USA, Inc.*, 441 F.3d at 4 (internal quotation marks omitted). Rather, Takeda contends that FDA has misapplied its own rules, arguing that FDA should have rejected Hikma's effort to rely on data for Col-Probenecid® (which is not subject to patent protection), because Colcrys® purportedly was the "most appropriate" drug for Hikma's application. Why so? For no other reason than that Colcrys® was available at the time of Hikma's filing.

But, again, FDA does not determine which specific drug an applicant should rely upon for each particular application. It only determines whether the applicant's reliance upon the particular drug was scientifically appropriate. Takeda has conflated the 505(b)(2) applicant's prerogative to "determine which listed drug(s) is most appropriate *for its development program*," (Reckitt Citizen Pet. Resp. at 3 (emphasis added)), with FDA's duty to ensure the sponsor's choice is "scientifically appropriate." *Id.* The statute and regulations allow an applicant to conduct its own studies to avoid referencing a particular product and its associated patents. *See, e.g.*, 21 U.S.C. § 355(b)(2)(B) (allowing applicants to seek approval for a label that does not even implicate "a method of use patent" for a listed drug); s*ee* Wong Decl., D.I. 16-9, Ex. A at 21 n.67; Guidance at 1-2. This is precisely what Hikma did here with its 505(b)(2) application for Mitigare™, as compared to other ANDA applicants who have sought to make a generic equivalent to Colcrys®.

Takeda points to nothing in the statute or any FDA regulation that required FDA to reject Hikma's application because it relied upon Col-Probenecid® instead of Colcrys®. Indeed, Takeda has to concede that Hikma's reliance on Col-Probenecid® is scientifically appropriate. After all, that is the exact same product Takeda itself relied on in its own 505(b)(2) application to convince FDA that Colcrys® is safe and effective for the prophylaxis indication. Woods Decl.,

D.I. 1-1, Ex. 6 at 9 ("Mutual is also relying upon the FDA's prior determination of safety and efficacy of colchicine for preventing gout flares (Col-Probenecid, ANDA 084-279)."). Hikma had no need to rely on Colcrys® to avoid "duplicate work," Guidance at 3, because Hikma does not rely on any of Takeda's data to support its application. Hikma's reliance on Col-Probenecid® did not somehow become less scientifically appropriate after the introduction of Colcrys®. *See* 21 C.F.R. § 314.54(a) (explaining that a 505(b)(2) "application need contain only that information needed to support the modification(s) of the listed drug"—such as "a new indication or new dosage form").

In particular, Hikma had no need to rely on Takeda's acute flare or DDI data, because none of this data appears in the Mitigare™ label, nor was inclusion of such data required to render Mitigare™ safe, as FDA concluded. *See* Wong Decl., D.I. 16-9, Ex. B (Mitigare™ Label); *see also* AR 113 ("Mitigare should not be used in this way."). And, because Col-Probenecid® is not associated with any patents, Hikma's application did not require any patent certification, much less a certification to Takeda's patents. *See* 21 C.F.R. § 314.54(a)(1)(vi). This basic statutory and regulatory analysis defeats Takeda's extraordinary request to deprive the public of a new drug deemed safe and effective by the federal agency tasked with making these determinations.

Takeda's true argument has no bearing on its claim that the APA has been violated—indeed, that argument already has been rejected. According to Takeda, Colcrys® is "the *only* single-ingredient oral colchicine product in 0.6 mg strength on the market" and, therefore, all generic colchicine products must reference Colcrys®—thus triggering a Paragraph IV certification and related litigation. Reply Br. 12, D.I. 22 (emphasis in original). FDA got it right the first time when, in 2011, it rejected the very same argument: "FDA denies Mutual's request

that any 505(b)(2) application for a single-ingredient oral colchicine product must necessarily cite Colcrys® as its listed drug." Wong Decl., Ex. A at 3, 20. As FDA explained, it "declines to speculate on whether a 505(b)(2) applicant . . . could submit adequate safety and effectiveness data to support approval without reference to Colcrys" in light of "the significant amount of non-product-specific published scientific literature . . . and additional non-product-specific literature that may become available over time." *Id.* at 21 (footnote omitted).

FDA's findings on this point in its 2011 citizen petition ruling and when approving Hikma's product was not only reasonable and correct, it is entitled to *Chevron* deference. *See Teva Pharm. USA, Inc.*, 441 F.3d at 4. That is no basis to disturb this agency conclusion.

III. A PERMANENT INJUNCTION IS BOTH IMPROPER AND UNNECESSARY

Takeda has failed to justify its request for a permanent injunction against FDA. Even if Takeda has shown that FDA acted arbitrarily (it has not), the "appropriate course" would be for this Court "to identify a legal error and then remand to the agency" for further consideration. *N. Air Cargo v. U.S. Postal Serv.*, 674 F.3d 852, 861 (D.C. Cir. 2012). Indeed, "[i]t [is] quite anomalous [for a district court] to issue an injunction" in an APA action, *id.*, as the statute "directs that [courts] 'shall . . . set aside [the] agency action'" found to be arbitrary or capricious. *R.J. Reynolds Tobacco Co. v. FDA*, 696 F.3d 1205, 1222 (D.C. Cir. 2012), *rev'd on other grounds by Am. Meat Inst. v. USDA*, 760 F.3d 18 (D.C. Cir. 2014) (en banc) (citing 5 U.S.C. § 706(2)). Given the district court's role as "an appellate tribunal" over the agency, a permanent injunction is almost never an appropriate remedy. *N. Air Cargo*, 674 F.3d at 861.

Even if it were, a permanent injunction "does not follow from success on the merits as a matter of course." *Winter v. Nat. Res. Def. Council, Inc.*, 555 U.S. 7, 32 (2008). Rather, "[a]n injunction should issue only if the traditional four-factor test is satisfied." *Id.* at 157. For all the

reasons discussed in Hikma's Opposition Brief, Takeda falls well short of the mark. Two reasons bear emphasis here.

First, Takeda has completely failed to show that it would suffer irreparable harm absent an injunction. It does not deny that the principal harm it would suffer from the launch of Mitigare™ is the loss of its ability to charge monopolistic prices on its product. But that is not enough. "[E]conomic loss qualifies [for an injunction] only if it 'threatens the very existence of the movant's business[.]'" *ViroPharma, Inc.*, 898 F. Supp. 2d at 25 (quoting *Wis. Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985) (per curiam)). Takeda has not produced a scintilla of evidence to demonstrate this, let alone enough to satisfy the high standard required for an injunction. Second, Takeda has failed to show that the public interest would be served by an injunction. As discussed in Part I, *supra* and as previously shown, "the [Mitigare™] label is safe"—in fact, "the Mitigare™ label recommendation is safer and more appropriate than . . . the one-size fits all approach of the Colcrys™ label." Hansten Decl., D.I. 16-2, at ¶¶ 15, 17; *see also* AR 672 (noting that there "was some discussion of whether the *Colcrys* labeling should be revised" in light of Hikma's studies (emphasis added)). Despite having the opportunity to do so, Takeda has produced nothing—save its own conjecture—to try to undermine that fact.

Ultimately, Takeda did not bring this case to protect the public from an "unsafe" drug. It brought this case to protect its own bottom line. Takeda has limited patents that cover a small fraction of the colchicine market. It now seeks to use those patents to shut out competition for the remaining, non-patented use of the drug—prophylaxis of gout flares. As a result, the price of this important medication has skyrocketed. It is now financially out of reach of many patients who sorely need it. That is the precise harm that the Hatch-Waxman Act is meant to cure. Congress created this regime "to get generic drugs into the hands of patients at reasonable

prices—fast." *In re Barr Labs., Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991). FDA has faithfully served that end by lawfully approving Mitigare™ after finding it to be safe and effective. Given the public's interest in "FDA . . . being able to discharge the duties entrusted to it by Congress free from judicial interference," *AstraZeneca Pharms. LP v. FDA*, 850 F. Supp. 2d 230, 249 (D.D.C. 2012), a permanent injunction—or any other relief, for that matter—is unwarranted.

CONCLUSION

For all of these reasons, the Court should deny Takeda's requests for temporary, preliminary and permanent injunctive relief, and further dismiss Takeda's complaint with prejudice.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I, Charles B. Klein, an attorney, hereby certify that on Friday November 14th, 2014, a true and correct copy of the foregoing motion, memorandum, and all exhibits thereto, was served via the Court's CM/ECF system on the following:

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