IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF 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.	Civil Action No. 1:14-cv-01668 FILED UNDER SEAL REDACTED

REDACTED

CONFIDENTIAL MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF PLAINTIFF'S MOTION FOR A TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION

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INTRODUCTION

Plaintiff Takeda Pharmaceuticals U.S.A., Inc. ("Takeda") seeks a TRO or preliminary injunction to stay FDA's recent unlawful approval of a prescription drug. On September 26, 2014, FDA approved an application submitted by Hikma Pharmaceuticals LLC ("Hikma") under Section 505(b)(2) of the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(b)(2) for permission to market Mitigare (colchicine) capsules, 0.6 mg, a single-ingredient oral colchicine product for the prophylaxis of gout flares.[1]

FDA's approval of Mitigare was unlawful, arbitrary and capricious for no fewer than three separate reasons. *First*, FDA acted arbitrarily and capriciously in approving Hikma's Section 505(b)(2) application for Mitigare without requiring the label to contain critical safety information that FDA itself previously determined was necessary for single-ingredient oral colchicine products. *Second*, FDA's approval of Hikma's application for Mitigare was unlawful, arbitrary and capricious because, as approved, Mitigare is not safe in light of the defects in its label. *Third*, FDA's failure to require Hikma to reference Takeda's own colchicine drug, Colcrys®, in its application interfered with Takeda's rights to participate in the administrative process, including the Paragraph IV certification process under Hatch Waxman and the Citizen Petition process. As a result, FDA's decision is unlawful, arbitrary, capricious, an abuse of discretion, and otherwise violates the Administrative Procedure Act (the "APA").

[1] Takeda became aware of the approval on September 30, 2014 from a Hikma press release of that date.

The four factors governing injunctive relief strongly favor issuance of an injunction in this case. First, Takeda's likelihood of success is strong. FDA's approval of Mitigare directly contradicts express determinations made by FDA regarding the appropriate labeling for single-ingredient oral colchicine products. Second, granting an injunction will promote the public interest by protecting patients from potentially severe, even fatal – and entirely unnecessary – safety risks associated with an inappropriately-labeled colchicine product. Third, in the absence of immediate injunctive relief, Takeda will suffer irreparable injury in the form of unrecoverable market share, reputational damage, and forgone procedural rights, including the 30-month stay afforded to pioneer drugs under the Hatch Waxman Act. Fourth, in contrast, the requested injunctive relief will cause no undue hardship to FDA or to Hikma, since it simply preserves the *status quo* pending briefing on the merits.

STATEMENT OF FACTS

1. Statutory Background

A. The New Drug Approval Process

The FDCA requires all new prescription drugs to obtain FDA approval before they can enter the marketplace. 21 U.S.C. § 355(a). Since 1984, the FDCA has permitted three types of applications for a new drug. At one end of the spectrum, a manufacturer can submit a full New Drug Application ("NDA") under Section 505(b)(1) of the FDCA. 21 U.S.C. § 355(b)(1). A full NDA is a comprehensive application used by brand-name or innovator companies. It contains results of well-controlled scientific studies conducted by or for the applicant, demonstrating that the drug is safe and effective. *Id.*

At the other end of the spectrum is the Abbreviated New Drug Application ("ANDA") under Section 505(j) of the FDCA. 21 U.S.C. § 355(j). ANDAs are used to obtain approval for generic versions of innovator drugs and generally do not include new clinical data. Instead, an ANDA relies on FDA's finding of safety and efficacy for a previously approved drug, which is known as the Reference Listed Drug ("RLD"). *See* 21 U.S.C. § 355(j)(2)(A). In other words, the point of an ANDA is not to demonstrate safety or effectiveness but to establish that the generic product is equivalent to an RLD already known to be safe and effective. *See id.*

With FDA's permission, an ANDA applicant may submit an ANDA for a product that differs from the RLD with respect to route of administration, dosage form, strength, or one active ingredient in a combination product. 21 U.S.C. § 355(j)(2)(C); 21 C.F.R. § 314.93. That permission is sought through a "suitability petition." 21 U.S.C. § 355(j)(2)(C). FDA will reject a suitability petition when the proposed modification would require new clinical data to show that the change does not affect safety or effectiveness. 21 C.F.R. § 314.93(e)(1)(iv). ANDA products are required to have the same labeling as the RLD, except for changes due to differences approved under a suitability petition and changes due to the fact that the ANDA product and RLD are produced or distributed by different manufacturers. 21 U.S.C. § 355(j)(2)(A)(v).

Between the two extremes of a full NDA and an ANDA lies a third option: an application submitted under Section 505(b)(2) of the FDCA. 21 U.S.C. § 355(b)(2). A 505(b)(2) application is a type of NDA and must directly demonstrate that the proposed drug product is safe and effective. *Id.* At the same time, a 505(b)(2) applicant does not have to conduct all of the burdensome scientific studies required of a full NDA. Instead,

the 505(b)(2) applicant can show safety and effectiveness by relying on studies that were not conducted by the applicant and for which the applicant does not have a right of reference. *Id.*

A 505(b)(2) application generally is used to seek approval of a drug that differs from a previously approved drug product. For example, a 505(b)(2) application may be used to seek approval of a drug product that has a different dosage form than the RLD. Verified Compl. Ex. 11 at 4. In this example, the applicant can rely on the investigative studies that were performed to obtain FDA approval for the previously approved product and new information needed to demonstrate the safety and effectiveness of the different dosage form. *Id.* at 3.

B. The Hatch-Waxman Patent Certification And Notice Process

Abbreviated applications both hasten the approval of new drugs and avoid unnecessary scientific testing by allowing the applicant to rely on what is already known about a drug. To balance the fact that ANDA and 505(b)(2) applicants can rely on data generated by innovator companies, Congress provided intellectual property protections for innovator products. In particular, the Hatch-Waxman amendments of 1984 create a process intended to ensure that patents covering an innovator drug are protected and that the innovator company receives notice of a relevant ANDA or 505(b)(2) application so that a patent infringement action can be initiated before the application is approved. *See* 21 U.S.C. § 355(b)(3)(A), 21 U.S.C. § 355(j)(2)(B).

When a drug is approved under an NDA, including a 505(b)(2) application, the drug and related patents are listed in an FDA publication called *Approved Drug Products with Therapeutic Equivalence Evaluations* (34th Ed. 2014), known as the "*Orange Book*."

If the product is the first-approved innovator of its kind, FDA will designate the product as the RLD for similar products. *See* 21 C.F.R. § 314.3(b) ("Reference listed drug means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application.").

When an applicant submits an ANDA, the application must identify the RLD on which the application relies. *See* 21 U.S.C. § 355(j)(2)(A)(i). Similarly, when an applicant submits a 505(b)(2) application, the application must identify the previously approved drug relied upon for approval, if any. 21 C.F.R. § 314.54. ANDAs and 505(b)(2) applications also must include certifications to the patents listed in the *Orange Book* for the referenced drug. *See* 21 U.S.C. §§ 355(b)(2)(A), 355(j)(2)(A)(vii). The applicant must certify that (i) no such patents exist, (ii) any such patents have expired, (iii) the proposed drug will not be marketed before the patent expires, or (iv) any such patents are invalid or will not be infringed by the proposed drug. *See, e.g.*, 21 U.S.C. § 355(b)(2)(A)(i) through (iv).

An ANDA or 505(b)(2) applicant that seeks FDA approval before a patent expires generally must submit a "Paragraph IV" certification – in keeping with paragraph iv of the statutory provision cited above – asserting that the patent is invalid or will not be infringed. *See* 21 U.S.C. § 355(b)(2)(A)-(B), 21 U.S.C. § 355(j)(2)(A)(vii)-(viii). Critically, whenever such an applicant submits a Paragraph IV certification, the applicant must promptly give notice to the manufacturer of the referenced drug and (to the extent there is a difference) to the owner of the relevant patents. *See, e.g.*, 21 U.S.C. § 355(b)(3)(A). Notice of a Paragraph IV certification must include certain information

regarding the application and a detailed statement of reasons why the patent is invalid or not infringed. *See, e.g.*, 21 U.S.C. § 355(b)(3)(D).

A Paragraph IV notice vests important statutory rights in the recipients. The submission of an ANDA or 505(b)(2) application seeking FDA approval during the term of a relevant patent is a technical act of patent infringement. *See* 35 U.S.C. § 271(e). If the patent holder or drug manufacturer brings an infringement action against the applicant within 45 days of receiving notice of the patent certification, FDA is statutorily prohibited from approving the application until 30 months have passed, the patents have expired, or a court has found the patents invalid or not infringed. *See* 21 U.S.C. §§ 355(c)(3)(C), 355(j)(5)(B)(iii). This 30-month period is built in to the statute to allow the patent issues to be adjudicated before launch of the follow-on product and the potential destruction of the innovator's market.

2. Colcrys® (colchicine) 0.6 mg Oral Tablets

On July 29, 2009, FDA approved Colcrys® oral tablets in 0.6 mg strength for the treatment of Familial Mediterranean Fever ("FMF"). Verified Complaint ¶ 22; Ex. 15. Because FMF is a rare disease, Mutual – the company that developed Colcrys® and then transferred rights to the product to Takeda – received for that indication seven years of orphan drug exclusivity, which expires on July 29, 2016. *Id.* ¶ 22; 21 U.S.C. § 360cc. On July 30, 2009, FDA approved Colcrys® for the treatment of acute gout flares. *Id.* ¶ 22; Ex. 13. Subsequently, on October 16, 2009, FDA approved Colcrys® for prophylaxis of gout flares. *Id.* ¶ 22; Ex. 14. Mutual used the 505(b)(2) pathway to receive approval for Colcrys ®, relying on its own clinical trials, literature, and a

previously approved drug product. *Id.* ¶ 22; Exs. 5, 13, 14, 15. FDA designated Colcrys® as an RLD. *Id.* ¶ 22; Ex. 16.

Colcrys® was the first single-ingredient oral colchicine product to receive marketing approval from FDA. Verified Complaint ¶ 24; Ex. 3. Although single-ingredient oral colchicine products were marketed before the approval of Colcrys®, such products were marketed without approved applications. Ex. 4. As a result of Mutual's innovative development to support the approval of Colcrys®, Mutual has obtained numerous patents directed to colchicine. In total, there are 17 patents listed in FDA's *Orange Book* for Colcrys®. Verified Complaint ¶ 23; Ex. 17.

Colchicine is a known toxin, and colchicine-containing drug products can have serious side effects if not properly administered. Verified Complaint ¶ 25; Ex. 4. Prior to Colcrys®'s approval, the oral colchicine tablets were sold by various manufacturers without approved applications were associated with significant adverse events, including death. *Id.*; Ex. 4. FDA was made aware of 751 reports of adverse events associated with colchicine toxicity – including 169 deaths associated with oral colchicine – through June 2007. *Id.*; Ex. 4. Of the 169 deaths, 117 of them were not reported as overdoses. *Id.* In other words, the majority of reported deaths had colchicine doses within the normal therapeutic range. Ex. 3 at 2. Furthermore, over half of the non-overdose reported deaths involved patients who were concomitantly using another drug called clarithromycin, indicating that drug-drug interactions may be related to toxicity. *Id.*

To support the safety and efficacy of Colcrys®, Mutual conducted two critical sets of clinical studies with the goal of reducing colchicine toxicity and related fatalities. Ex.

3. First, Mutual studied drug-drug interactions. *Id.* at 2. Second, Mutual studied whether a lower colchicine dose could be effective to treat gout flares. *Id.* at 2-3.

***Drug-Drug Interactions*:** To study drug-drug interactions, Mutual conducted at least eight studies comparing the bioavailability of colchicine administered alone with the bioavailability of colchicine co-administered with other drugs. Ex. 5. Such drugs included cytochrome P450 3A4 ("CYP3A4") inhibitors, protease inhibitors, and P-glycoprotein (P-gp") inhibitors, all of which can affect the mechanisms that the body uses to metabolize colchicine and thus can lead to toxic amounts of colchicine. *Id.* at 17.

Mutual discovered that co-administering colchicine and such drugs significantly raises colchicine levels in the blood. For example, the co-administration of clarithromycin, a commonly used antibiotic, can cause colchicine blood levels to increase by approximately 250% percent. Ex. 5 at 17. Based on its studies, Mutual also developed a safe way to dose colchicine concomitantly with such drugs, including clarithromycin. The dose adjustments are critically important from a public health perspective. In particular, as noted above, over half of the deaths attributed to oral colchicine taken within therapeutic limits involved patients who were concomitantly using clarithromycin.

Based on Mutual's drug-drug interaction studies, the label for Colcrys® includes several detailed tables that provide specific dose adjustments for patients who take colchicine with CYP3A4 inhibitors, P-gp inhibitors, or protease inhibitors. Ex. 5 (Colcrys® Label) at 5-6. In its review of Colcrys®, FDA stated that the new dose adjustments are "necessary" to compensate for the increase in colchicine exposure. In particular, FDA stated:

> *Strong CYP3A4 inhibitors increase colchicine systemic exposure by 3- to 4-fold. Hence, a 75% decrease in dose is necessary to compensate for the increase in exposure.*
>
> *Moderate CYP3A4 inhibitors cause a 2-fold increase in colchicine AUC when coadministered. Hence, a 50% decrease in dose is necessary to compensate for the increase in exposure.*
>
> *P-gp inhibition by cyclosporine resulted in 3.5-fold increase in Cmax and AUC of colchicine. Hence, a 75% decrease in dose is necessary to compensate for the increase in exposure.*

Ex. 6.

Underscoring the importance of Mutual's work, FDA issued an FDA Alert when Colcrys® was approved to inform healthcare providers and the general public of the significant new safety information regarding the administration of colchicine. The FDA Alert notes that the Colcrys® label contains dose adjustments to reduce the risk of drug-drug interactions and recommends that healthcare professionals "refer to Colcrys' approved prescribing information for specific dosing recommendations and additional drug interaction information." Ex. 3 at 1.

Mutual's work in identifying and resolving potentially fatal drug-drug interactions for colchicine has been deemed so important by FDA that FDA incorporated it into the labeling for other drugs as well. *Id*.; Ex. 7. In particular, one of Mutual's studies demonstrated that the co-administration of colchicine with the protease inhibitor ritonavir could increase colchicine blood levels by nearly 185%. *Id.* As a result of this work, FDA took the significant step of requiring the labeling for *all* protease inhibitors approved for the treatment of HIV-1 infection (such as Norvir (ritanovir) and Invirase (saquinavir mesylate)) to include Mutual's reduced dosing recommendations for co-administering these drugs with colchicine. *Id*.; Ex. 7.

***Lower Dose Colchicine*:** In addition to drug-drug interactions, Mutual also studied whether a low-dose regimen is effective for the treatment of acute gout flares. Historically, the recommended dose of colchicine for the treatment of acute gout flares was 1.2 mg of colchicine followed by 0.6 mg every hour until the flare resolves or until gastrointestinal toxicity occurred, a regimen that could result in a total dose of about 4.8 mg. Ex. 3 at 2. In contrast, Mutual developed a low-dose regimen consisting of 1.2 mg followed by 0.6 mg one hour later, which provides a total dose of 1.8 mg. *Id.*

Mutual designed and conducted a multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-comparison trial in which 185 adults (out of a total of 575 trial participants) were exposed to a high-dose regimen of colchicine, a low-dose regimen of colchicine, or a placebo regimen. Ex. 8. Mutual's trial was referred to as the Acute Gout Flare Receiving Colchicine Evaluation ("AGREE") Trial. *Id.*

Mutual's trial demonstrated that Mutual's new low-dose regimen for Colcrys® is just as effective for treating gout flares but simultaneously reduces the risk of adverse events compared to the traditional high-dose regimen. Ex. 8. For example, ten trial participants receiving the high dose of colchicine experienced severe adverse events; *zero* participants receiving the low dose of colchicine did so. *Id.* at 67. As another example, the rate of less-severe gastro-intestinal adverse events (e.g., diarrhea, nausea or vomiting) was just 26% in low-dose subjects compared to 77% in high-dose subjects. *Id.* at 69. AGREE showed that patients have historically been given between two and four times the necessary colchicine dosage to achieve the desired effect. FDA highlighted the significant safety improvement provided by Mutual's new low-dose regimen in its FDA Alert. Ex. 3 at 3.

3. West-Ward's Application And Mutual's Citizen Petition

During the fall of 2010, Mutual learned through public sources that Hikma's U.S. manufacturer, West-Ward Pharmaceutical Corp., had submitted an application to FDA for a single-ingredient oral colchicine product. The FDA application process is confidential, and Mutual did not know the details of the application. However, Mutual surmised that West-Ward's application was for a duplicate generic version of Colcrys®. Accordingly, Mutual expected to be cited as the RLD for West-Ward's application and expected to receive a patent certification notice. Even if West-Ward's application was not for a duplicate version of Colcrys®, Mutual still expected that Colcrys® would be cited as a reference drug because the application would have to rely on the new drug-drug interaction and low-dose information developed by Mutual.

Mutual did not receive any notice of patent certification. Accordingly, in November 2010, Mutual filed a Citizen Petition with FDA requesting that FDA ensure that any application seeking approval for a duplicate version of Colcrys® be submitted as an ANDA and not a 505(b)(2) application. Ex. 9. Mutual's Citizen Petition requested, among other items, that FDA "[r]equire the labeling for any single-ingredient oral colchicine product to include all information related to drug-drug interactions that is in the Colcrys labeling, including relevant dose adjustments needed to prevent unnecessary toxicity." *Id.*

4. FDA's Response To Mutual's Citizen Petition

FDA granted the major actions requested in Mutual's Citizen Petition. Ex. 1. FDA confirmed that West-Ward had inappropriately submitted a 505(b)(2) application for a duplicate version of Colcrys® and that the application must be withdrawn and

resubmitted as an ANDA. In its response, FDA acknowledged that it had previously advised West-Ward that West-Ward could submit a 505(b)(2) application. FDA stated that "FDA regrets that its advice to West-Ward . . . and subsequent filing of West-Ward's 505(b)(2) application were incorrect." *Id.* at 17. Additionally, FDA stated that it intends to supplement its training within "appropriate components" in the agency regarding the appropriate availability of 505(b)(2) applications. *Id.* at n.58.

FDA also agreed with Mutual regarding the critical importance of the drug-drug interaction information Mutual had developed. Specifically, FDA stated that "FDA agrees 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." Ex. 1 at 3. After noting the risk for severe drug interactions, FDA concluded that the new dosing recommendations will help mitigate the risk. *Id.* at 19. Importantly, FDA acknowledged that:

> Before the approved labeling for Colcrys, there were no widely-accepted specific recommendations for dose reduction in the setting of potential concomitant use of drugs with known interactions, other than avoidance when possible and caution when necessary, with vigilant monitoring of clinical signs of toxicity.

Id.

Furthermore, FDA concluded that the labeling for *any* single-ingredient colchicine product for prophylaxis of gout flares must include the new low-dose regimen for treating acute gout flares because prophylactic patients may develop an acute gout flare and the new low dose is essential to avoiding cumulative toxicity from combining the treatments for prophylaxis and acute gout flares. In particular, FDA stated:

> To the extent that a healthcare provider determines it is necessary to use colchicine for treatment of an acute gout flare in a patient receiving colchicine for prophylaxis, adequate information about potential toxicity of colchicine dosing

> would be important to minimize the risk of cumulative toxicity. Accordingly, the labeling for a single-ingredient colchicine product seeking approval for prophylaxis of gout flares should 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.

Ex. 1 at 24 (footnotes omitted).[2]

5. FDA's Approval of Mitigare

Over three years passed. Then, without notice or warning, on September 26, 2014, FDA approved Hikma's colchicine product, Mitigare, which is a 0.6 mg oral capsule. Ex. 10 (Letter from B. Chowdhury to Hikma Pharmaceuticals LLC at 1 (September 26, 2014)). Mitigare is indicated only for the prophylaxis of gout flares. *Id.* According to FDA's approval letter, Mitigare was submitted under a 505(b)(2) application and not an ANDA through a suitability petition. *Id.* As a capsule, Mitigare is not an exact duplicate of Colcrys®. Apparently, instead of resubmitting its previous application for a duplicate colchicine product as an ANDA, Hikma reformulated the product to have a different dosage form and submitted it – again – under a 505(b)(2) application.

Despite FDA's response to Mutual's Citizen Petition, the label for Mitigare does not include the Colcrys® drug-drug interaction dose adjustments. Rather, the label for Mitigare states:

> Inhibition of both CYP3A4 and P-gp by dual inhibitors such as clarithromycin has been reported to produce life-threatening or fatal colchicine toxicity due to significant increases in systemic colchicine levels. Therefore, concomitant use of

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[2] FDA stopped short of determining that any single-ingredient oral colchicine product that is not a duplicate of Colcrys® must reference Colcrys®. According to FDA, such a determination "will depend on the facts and circumstances of the particular application and a blanket refusal to review any such application is not warranted at this time." Ex. 1 at 21.

> MITIGARE™ and inhibitors of CYP3A4 or P-glycoprotein should be avoided [See Drug Interactions (7)]. If avoidance is not possible, reduced daily dose should be considered and the patient should be monitored closely for colchicine toxicity.

Ex. 2 at 2.

Similarly, the label for Mitigare also omits Colcrys®'s new low-dose regimen for treating acute gout flares. Although Mitigare is not indicated for acute gout flares, FDA had also concluded that even a single-ingredient colchicine product indicated only for prophylaxis still must include the low-dose regimen for acute gout flares because of the potential for cumulative toxicity when treating patients for both prophylaxis and acute flares. Ex. 1 at 24. However, the label for Mitigare simply states that "[t]he safety and effectiveness of MITIGARE™ for acute treatment of gout flares during prophylaxis has not been studied." Ex. 2 at 1, 2.

As with the previous 505(b)(2) application, Hikma apparently did not reference Colcrys® because the Mitigare label omits the new safety innovations developed for Colcrys®. Thus, the application did not include any certification to the patents listed for Colcrys®, which allowed Hikma to avoid the notification and 30-month stay provisions. And because the FDA application process otherwise is confidential, the first that Takeda – Mutual's corporate successor – learned of Mitigare's approval was following the September 26 approval letter itself.

THE NEED FOR IMMEDIATE JUDICIAL INTERVENTION

FDA's actions pose a substantial and imminent harm to prospective patients who will be placed on Mitigare. The label FDA approved for Mitigare lacks critical information regarding low-dose treatment for acute gout and the drug-drug interaction

dosing adjustments, directly contradicting its earlier findings and admonitions. Verified Complaint ¶¶ 42-43; Woods Decl. ¶ 10; Ex. 2. Labeled in this manner, Mitigare poses a very real risk of causing patients severe harm, including death from drug-drug interactions and colchicine toxicity. Verified Complaint ¶ 61; Wood Decl. ¶ 30; Exs. 2, 3. Because FDA's approval opened the door for Hikma to launch Mitigare at any time, and Hikma did in fact launch Mitigare as a branded product on October 3, 2014, the threat to patients is imminent. Verified Complaint ¶¶ 45-61; Woods Decl. ¶ 30.

FDA's actions will also irreparably harm Takeda. Instead of following its own previous proclamation about the necessity of including drug-drug interaction dosing adjustments and low-dosage regimen safety information in labeling for single-ingredient colchicine products, FDA left the Mitigare label devoid of the detailed dosing guidelines. FDA allowed general statements that the dose should be reduced and that the safety and effectiveness for treatment of gout flares during prophylaxis "has not been studied." Verified Complaint ¶¶ 42-43; Ex. 2. This action dispensed with the need for Hikma to reference Colcrys® as the RLD and certify to the patents listed for Colcrys®. 21 U.S.C. § 355(b)(2)(A). Had Hikma certified to these patents, the patent certifications necessarily would have included a Paragraph IV certification, which in turn would have required Hikma to notify Takeda of the pending application. *See* 21 U.S.C. § 355(c)(3)(C). Such notice would have triggered patent litigation and, consequently, a statutorily mandated 30-month stay of Hikma's application. *See* U.S.C. §§ 355(c)(3), 355(j)(5)(B)(iii). Takeda is entitled to pursue those statutory rights and should be permitted to do so prior to Hikma's launch of Mitigare.

In addition, because Hikma was not required to file a Paragraph IV certification, Takeda was deprived of the opportunity to file a Citizen's Petition in advance of Mitigare's approval. If FDA had complied with its governing regulations and statutory mandate, Takeda would have received notice of the pending application under the Hatch-Waxman Act. Now, though, it is too late because petitioning the FDA post-launch would be futile. For these reasons, Takeda will suffer a procedural harm at the hands of FDA that is irreparable absent immediate judicial intervention.

Takeda also will suffer irreparable harm absent entry of a TRO. It will suffer irreparable reputational harm from any injuries or fatalities resulting from the Mitigare label's lack of detailed drug-drug interaction and low-dosage safety information being unfairly imputed to Colcrys®. Verified Complaint ¶ 63. It will suffer significant loss of goodwill and harm to the company reputation from the perception that Takeda is causing a generic product to be taken off the market. Woods Decl. ¶ 66. It will also suffer financial harm from the devastating market impact on Takeda. Within the first four weeks, Mitigare's entry to the market will cause Takeda to lose between [redacted] of the number of Colcrys® prescriptions that would otherwise be written and filled, and within the first twelve months, it would cause Takeda to lose [redacted] of these prescriptions. Woods Decl. ¶¶ 57-60. That financial harm will have ripple effects. Among other things, the significant loss of revenue will irreparably harm [redacted] *Id.* ¶¶ 23, 69-71. The market impact just described would not be reversible if Mitigare is later taken off the market because of several market forces specific to Colcrys®. *Id.* ¶¶ 63-68.

Additionally, Takeda has expended [redacted] to develop, patent, and promote Colcrys®, and would lose the value of its investment if a generic single-ingredient oral colchicine product were permitted to prematurely enter the market. *Id.* ¶ 22.

There is no mechanism by which Takeda can be made whole for the injury that would result from the entry into the marketplace of Hikma's Mitigare drug. Judicial intervention therefore is necessary to prevent devastating harm.

ARGUMENT

The standards governing issuance of a temporary restraining order ("TRO") or preliminary injunction are well known. *See Morgan Stanley DW Inc. v. Rothe,* 150 F. Supp. 2d 67, 72 (D.D.C. 2001). The movant must show: "(1) a substantial likelihood of success on the merits, (2) that it would suffer irreparable injury if the injunction is not granted, (3) that an injunction would not substantially injure other interested parties, and (4) that the public interest would be furthered by the injunction." *See Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1066 (D.C. Cir. 1998) (citation omitted). All four of these factors mandate entry of a TRO here.

I. PLAINTIFF HAS A STRONG LIKELIHOOD OF SUCCESS ON THE MERITS.

The APA provides that a court "shall . . . hold unlawful and set aside agency action, findings, and conclusions found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). It is well settled that agency action is arbitrary and capricious where, as here, it deviates from agency precedent without reasoned explanation. *See, e.g., Lone Mtn. Processing, Inc. v.*

Sec'y of Labor, 709 F.3d 1161, 1164 (D.C. Cir. 2013) (finding action arbitrary and capricious where agency "failed to even mention or discuss, let alone distinguish" prior orders); *Friedman v. Sebelius*, 686 F.3d 813, 828 (D.C. Cir. 2012) (finding agency decision arbitrary and capricious because "it failed to explain its departure from the agency's own precedents"); *Fox v. Clinton*, 684 F.3d 67, 80 (D.C. Cir. 2012) (finding agency's action to be "arbitrary and capricious for want of reasoned decisionmaking"). Courts also have widely recognized that an agency decision is arbitrary and capricious if the agency "offered an explanation for its decision that runs counter to the evidence before the agency." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43, 103 S. Ct. 2856, 2867 (1983); *see also Clark County, Nevada v. FAA*, 522 F.3d 437, 441-42 (D.C. Cir. 2008). The same is true where any agency ignores evidence bearing on the issue before it. *Butte County, Cal. v. Hogen*, 613 F.3d 190 (D.C. Cir. 2010).

Judicial review of agency action requires a "searching and careful" inquiry into the basis for the agency's decision. *Zotos Int'l, Inc. v. Young*, 830 F.2d 350, 352 (D.C. Cir. 1987). The reviewing court may give deference to an agency's scientific judgments to the extent they are consistent and reasonable, but the court does "not hear case merely to rubber stamp agency actions. To play that role would be tantamount to abdicating the judiciary's responsibility under the Administrative Procedure Act." *Natural Res. Def. Council, Inc. v. Daley*, 209 F.3d 747, 755 (D.C. Cir. 2000) (quotation omitted). While courts often defer to an agency's substantiated scientific judgments, the emphasis is very much on "substantiated." Mere assertions of agency expertise will not do; the agency must show its work.

FDA fails all of those tests here, for three separate reasons. First, FDA acted arbitrarily and capriciously in approving Hikma's Section 505(b)(2) application for Mitigare without requiring the label to contain critical safety information that FDA previously stated was necessary for single-ingredient oral colchicine products. Second, FDA's approval of Hikma's application for Mitigare is arbitrary and capricious and an abuse of discretion because, as approved, Mitigare is not safe in light of the defects in its label, as FDA itself found previously. Third, FDA's failure to require Hikma to reference Colcrys® in its application interfered with Takeda's rights to participate in the administrative process, including the Paragraph IV certification process under Hatch Waxman and the Citizen Petition process.

A. FDA Acted Arbitrarily and Capriciously by Approving Hikma's Product Without Critical Safety Information that FDA Previously Stated was Necessary for Single-Ingredient Oral Colchicine Products.

FDA has previously concluded that product labeling for any single-ingredient oral colchicine products such as Mitigare must include certain safety information that Mitigare's labeling indisputably omits. FDA's response to Mutual's 2011 Citizen Petition concluded 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*." Compl. Ex. 1 at 3, 19-20 (emphases added). This is because "there is a risk for severe drug interactions in certain patients treated with colchicine and concomitant P-gp or strong CYP3A4 inhibitors[,] and the new dosing recommendations for concomitant use will help mitigate this risk." *Id.* at 19.

Mitigare's label fails to include these dose adjustments.[3] Instead, it states only that concomitant use of Mitigare and inhibitors of CYP3A4 or P-gp "should be avoided due to the potential for serious and life-threatening toxicity" and that if co-administration is necessary, the dose of Mitigare should be reduced and the patient should be monitored. Ex. 2 at Section 5 (p 2-4).

FDA also has observed that "the labeling for a single-ingredient colchicine product seeking approval for prophylaxis of gout flares should 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." Compl. Ex. 1 at 3, 24. In particular, FDA acknowledged that the use of colchicine for prophylaxis of gout flares "increases the susceptibility to toxicity related to additional doses of colchicine." *Id.* at 24. Accordingly, FDA agreed that even a product indicated only for prophylaxis needs to include the low-dose treatment for acute gout flares because "adequate information about potential toxicity of colchicine dosing would be important to minimize the risk of cumulative toxicity" in this situation. *Id.* Indeed, the Colcrys® labeling includes several statements regarding how to safely treat an acute gout flare that develops in a patient taking colchicine for prophylaxis.[4] Again, Mitigare's label

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[3] If FDA had required Hikma to submit an ANDA under a suitability petition instead of allowing a 505(b)(2) application, then Mitigare would have been required to have the same labeling as Colcrys® and could not have omitted critical safety information from its labeling, such as the drug-drug interaction dosing adjustments described in the Colcrys® labeling. *See* 21 U.S.C. § 355(j)(2)(A)(v).

[4] *See, e.g.,* Ex. 5 at 3 ("COLCRYS may be administered for treatment of a gout flare during prophylaxis at doses not to exceed 1.2 mg (two tablets) at the first sign of the flare followed by 0.6 mg (one tablet) one hour later. Wait 12 hours and then resume the prophylactic dose.")

fails to contain the information that FDA indicated was "important" and should be included. Instead, the label simply states that "the safety and effectiveness of Mitigare for acute treatment of gout flares during prophylaxis has not been studied." Ex. 2 at 1.[5]

Where, as here, an agency reverses course on an issue of science or policy, it is required to supply a reasoned basis for the change. *See, e.g.*, *Lone Mtn. Processing, Inc. v. Sec'y of Labor*, 709 F.3d 1161, 1164 (D.C. Cir. 2013) (finding action arbitrary and capricious where agency "failed to even mention or discuss, let alone distinguish" prior orders); *Friedman v. Sebelius*, 686 F.3d 813, 828 (D.C. Cir. 2012) (finding agency decision arbitrary and capricious because "it failed to explain its departure from the agency's own precedents"); *Fox v. Clinton*, 684 F.3d 67, 80 (D.C. Cir. 2012) (finding agency's action to be "arbitrary and capricious for want of reasoned decisionmaking"); *Ramaprakash v. F.A.A.*, 346 F.3d 1121, 1125 (D.C. Cir. 2003) ("Agencies are free to change course as their expertise and experience may suggest or require, but when they do so they must provide a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored.") (quotations omitted); *Action for Children's Television v. F.C.C.*, 821 F.2d 741, 745 (D.C. Cir. 1987) (same). As the

[5] Additionally, FDA requires the labeling of all protease inhibitors approved for treatment of HIV-1 infection to include reduced dosing instructions for the co-administration of these drugs with colchicine. FDA For Consumers, "New label information affecting all approved protease inhibitors for treatment of HIV" (Apr. 27, 2010). This is because Mutual's studies concluded that the co-administration of colchicine with the protease inhibitor ritonavir could increase average colchicine blood levels by nearly 185%, with some patients having increased levels approaching 450%. Similar to the protease inhibitor labeling, FDA also authorized the Colcrys® labeling to include information about reduced dosing for co-administration with protease inhibitors. Ex. 5. But Mitigare's labeling contains no such information.

Supreme Court noted in *F.C.C. v. Fox Television Stations, Inc.*, 129 S. Ct. 1800, 1811 (2009):

> [T]he agency need not always provide a more detailed justification than what would suffice for a new policy created on a blank slate. Sometimes it must – when, for example, its new policy rests upon factual findings that contradict those which underlay its prior policy. . . . It would be arbitrary or capricious to ignore such matters. In such cases it is not that further justification is demanded by the mere fact of policy change; but that *a reasoned explanation is needed for disregarding facts and circumstances that underlay or were engendered by the prior policy*. (citations omitted) (emphasis added).

FDA's approval of Mitigare and the accompanying label amounts to an abrupt about-face of its previous position that labeling for such products must include information about drug interactions and dose adjustments to prevent toxicity. Far from providing a reasoned explanation for disregarding the toxicity concern addressed by its previous statements and policies, FDA has provided no justification whatsoever for abandoning these requirements. It is arbitrary and capricious for FDA to ignore, without explanation, its previous conclusions that 1) the dosing recommendations for concomitant use of colchicine and P-gp or strong CYP3A4 inhibitors "will help mitigate th[e] risk" of "severe drug interactions," Verified Complaint Ex. 1 at 3, 19, and 2) "the labeling for a single-ingredient colchicine product seeking approval for prophylaxis of gout flares should inform healthcare providers that the lower dose colchicine regimen . . . is adequate to treat an acute gout flare that may occur during chronic colchicine use" in order to "minimize the risk of cumulative toxicity." *Id.* at 3, 24.

B. FDA's Approval of Mitigare Was Arbitrary and Capricious and An Abuse of Discretion Because, As Approved, Mitigare Is Not Safe.

Pursuant to the FDCA, a new drug cannot be marketed unless FDA determines the drug to be safe and effective for its intended use. 21 U.S.C. § 355(a); *see generally Food and Drug Admin. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000). As approved, Mitigare is not safe in light of the significant deficiencies in its labeling described above.

In connection with its review and ultimate approval of Colcrys® in 2009, FDA conducted an analysis of its Adverse Event Reporting System (AERS) and the medical literature. That analysis "revealed cases of fatal colchicine toxicity reported in certain patients taking standard therapeutic doses of colchicine and concomitant medications that interact with colchicine, such as clarithromycin." Verified Complaint Ex. 1 at 7.[6] The agency identified 169 deaths associated with the use of unapproved oral colchicine products, many of which were linked to the simultaneous use of colchicine and clarithromycin, a widely-used antibiotic. *Id.*

This review process leading to FDA's approval of Colcrys® marked a dramatic shift in the agency's regulation of colchicine drugs. Prior to the approved labeling for Colcrys®, no widely-accepted recommendations existed for dose reduction in the context of concomitant use of colchicine and drugs with known interactions; instead, the common

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[6] Colchicine has long been recognized as having dose-related toxicity. Verified Complaint Ex. 1 at 5. The most common toxicity is gastrointestinal – nausea, vomiting, diarrhea, abdominal pain. *Id.* Gastrointestinal toxicity may be followed by bone marrow suppression, renal failure, seizures, and sensorimotor neuropathy, among other symptoms. *Id.*

directive was "avoidance when possible and caution when necessary, with vigilant monitoring of clinical signs of toxicity." *Id.* at 19. However,

> [a]s knowledge of the drug interaction potential of the P-gp pathway has accumulated, it has also been recognized that P-gp inhibitors (such as cyclosporine) have the potential to dangerously interact with colchicine. Over the last several years, 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 (i.e., for chronic gout).

Id. Moreover, "Mutual's drug-drug interaction studies provided new, quantitative information about the extent of changes in exposure that can occur with co-administration of certain drugs with colchicine." *Id.*

Based on FDA's "review of a significant volume of published literature as well as Mutual's . . . drug-drug interaction studies[,]" it identified risks for severe drug interactions in some patients treated with colchicine and certain inhibitors. *Id.* FDA stated that the dosing recommendations approved in the Colcrys® label "will help mitigate this risk." *Id.*; *see also id.* at 7.

Unsurprisingly then, as noted above, FDA required that "product labeling for any single-ingredient oral colchicine product . . . include adequate information on drug-drug interactions, including relevant dose adjustments needed to prevent unnecessary toxicity." *Id.* at 3, 19-20. In light of the significance of these safety concerns, on July 30, 2009, FDA also issued a drug safety communication for healthcare professionals in connection with the approval of Colcrys®. Verified Complaint, Ex 3. This communication described "important safety information" about drug interactions with certain inhibitors, including cases of fatal colchicine toxicity, and referred medical

professionals to the dosing recommendations and additional drug interaction information in the Colcrys® product labeling. *Id.* at 1-2; *see also* Verified Complaint, Ex. 1 at 7.

FDA's hasty approval of Mitigare improperly ignores these lessons. *Hogen*, 613 F.3d at 194 ("an agency cannot ignore evidence contradicting its position"). As approved, Mitigare is not "safe" because its labeling does not reflect these safety concerns—concerns the agency itself uncovered and repeatedly emphasized. Verified Complaint, Ex. 1 at 16 (noting that "the requirements for approval of a single-ingredient colchicine product have changed based on the safety concerns identified during review of the Colcrys 505(b)(2) application"). The Mitigare label contains neither the FDA-approved low-dose-treatment notation for acute gout nor the drug-drug interaction dosing adjustments, *see* Verified Complaint, Ex. 2, both of which FDA expressly required in light of the severe safety concerns it identified during the Colcrys® review process. Verified Complaint, Ex. 1 at 3, 19-20, 24. Indeed, FDA later observed that without the discoveries of the Colcrys® review process, "outdated assumptions of what is safe and effective for treatment with oral colchicine would have remained unchecked, and patients would have continued to suffer from adverse reactions such as severe gastro-intestinal complications – and even death – needlessly." *Id*. at 8. The Mitigare label as approved perpetuates these "outdated assumptions" by omitting key safety information. Abusing its discretion and arbitrarily and capriciously jettisoning its own requirements and ignoring key safety information, FDA approved Mitigare despite the fact that it is not safe.

C. FDA's Approval of Mitigare Violated FDA's Own Procedural Requirements

FDA's failure to require Hikma to reference Colcrys® in its application also violated the agency's own procedural requirements for drug approval. Had the proper procedures been followed, Takeda would have been entitled to participate in (i) the Paragraph IV certification process and (ii) the Citizen Petition process.

Despite FDA's previous proclamation about the necessity of including drug-drug interaction dosing adjustments and low-dosage regimen safety information, the Mitigare label was devoid of that information. Verified Complaint, Ex. 2. Had such information been required, Hikma would have had to reference Colcrys® and certify to the patents listed for Colcrys®. See 21 U.S.C. § 355(b)(2)(A).

In particular, the drug-drug interaction dosing adjustments and low-dosage regimen were developed based on studies of Colcrys® and was approved under the Colcrys® NDA. Had Hikma included the information in Mitigare's labeling, in the manner outlined in FDA's Colcrys® Response, Hikma would have been required under the FDCA to provide clinical data to support the labeling statements. The FDCA provides several options for a sponsor, like Hikma, that wants to compete in the same market as the pioneer sponsor, Takeda, with labeling that is as safe as that of the pioneer product.

First, Hikma could have conducted its own clinical studies. On the drug-drug interaction issue, Hikma did conduct several pharmacokinetic-type studies (studies that measure the amount of drug in the blood), but those studies do not support Hikma's final labeling. Hikma's studies failed to show a drug-drug interaction with most of the drugs studied. Yet, the labeling for Mitigare recommends that patients avoid taking Mitigare

with inhibitors of CYP3A4 or P-glycoprotein or, if avoidance is not possible, then reduced daily dose should be considered. Ex. 2 at 2. On the gout flare issue, Hikma acknowledges in the Mitigare labeling that "The safety and effectiveness of Mitigare™ for acute treatment of gout flares during prophylaxis has not been studied." *Id.* Thus, Hikma lacks its own data to support any labeling statements on the drug-drug interaction issue and the low dose regimen for treating acute gout flares.

Second, Hikma could have relied on literature instead of conducting its own studies. However, for the literature to be adequate to support FDA-approved labeling, the literature must report on adequate and well-controlled clinical studies. Moreover, if the literature identifies an FDA-approved drug product, the person relying on the literature must certify to any patents that claim the approved product and must follow the notification requirements under 505(b)(2). Ex. 11 at 8. Takeda is not aware of published literature that would support the safety information set forth in the Colcrys® labeling regarding proper dose adjustments to prevent potentially fatal drug-drug interactions and proper dosing during a gout flare, other than literature that reports on studies of Colcrys®.

Finally, an applicant may reference a previously approved drug product to obtain the benefit of FDA's prior review and approval of another sponsor's clinical data. In this instance, the studies and information are available for reference only under the Colcrys® NDA, provided the requirements of section 505(b)(2) are followed. Indeed, FDA even stated that "[b]efore the approved labeling for Colcrys, there were no widely-accepted specific recommendations for dose reduction in the setting of potential concomitant use of drugs with known interactions, other than avoidance when possible and caution when

necessary, with vigilant monitoring of clinical signs of toxicity." Colcrys® Response at 19.

Thus, unless Hikma was willing to support its own labeling with its own data, to obtain approval for evidence-supported labeling under the FDCA, it must reference the necessary clinical data, either from the literature or from a previously approved drug product. At present, Colcrys® is the only approved drug product that includes data and labeling sufficient to meet the safety standard outlined in FDA's Colcrys® Response.[7] In fact, FDA specifically recommended that healthcare providers refer to the Colcrys® labeling for specific dosing recommendations and drug interaction information. FDA Alert at 1.

Had Hikma referenced Colcrys® and thus certified to the patents listed for Colcrys® in FDA's *Orange Book*, the patent certifications likely would have included a Paragraph IV certification, which in turn would have required Hikma to notify Takeda of the pending application. *Id.* Such notice would necessarily have triggered patent

[7] Prior to Mitigare, Colcrys® was the only single-ingredient oral colchicine product approved by FDA. FDA's *Orange Book* lists only two other currently marketed products that contain colchicine, both of which contain colchicine in combination with another drug, probenecid. The combination products were approved by FDA under ANDAs rather than NDAs. *See* Orange Book (34th ed. 2014) listing ANDA 84279 and ANDA 40618. Therefore, these products would not be considered appropriate for reference in a 505(b)(2) application because ANDAs do not contain clinical data and do not require an FDA finding of safety and effectiveness based on clinical data submitted in support of these applications. *See* 21 C.F.R. § 314.54 (requiring identification of a "listed drug for which FDA has made a finding of safety and effectiveness"). Referencing these ANDA products would not add to the adequate and well-controlled clinical studies needed to support Hikma's 505(b)(2) application. It is also apparent, when comparing the Mitigare labeling with Colcrys®, that the Mitigare labeling follows the text and format of the Colcrys® labeling, except for the omitted safety information discussed in the body of this memorandum. The combination colchicine-probenecid products are approved for the treatment of gout, including recurrent acute attacks of gout, but these products have their own unique labeling.

litigation and consequently a statutorily mandated 30-month stay of Hikma's application. *See* 21 U.S.C. §§ 355(c)(3); 355(j)(5)(B)(iii). In plain language: FDA's failure to enforce its own labeling requirements allowed Hikma to circumvent the statutory directive that it file a Paragraph IV certification to Takeda's patents, thus keeping Hikma's application confidential from Takeda. As a result, Takeda never had the opportunity to file patent claims under Hatch Waxman prior to Mitigare's approval, nor to take advantage of the resulting 30-month stay of Mitigare's approval.

In addition, FDA's procedural violation deprived Takeda of the opportunity to file a Citizen's Petition in advance of Mitigare's approval. Under 20 C.F.R. § 10.30, any person or entity, including pharmaceutical companies, may file a citizen petition asking FDA to refrain from taking an administrative action. But here, Takeda never had the opportunity, because it had no notice of the pending application until it had been approved.

II. THE PUBLIC INTEREST FAVORS THE REQUESTED RELIEF.

The public interest plainly favors granting an injunction here. First, the public has an interest in ensuring the safety and efficacy of drugs. The public's interest is particularly keen in this case because, barring a TRO, FDA's actions will usher into the marketplace a drug that does not meet statutory – indeed, FDA's own – standards designed to protect patients' health and safety.

The public also has an unmistakable interest in seeing that laws are faithfully executed by public officials. *Fund for Animals, Inc. v. Espy*, 814 F. Supp. 142, 152 (D.D.C. 1993) ("there is a strong public interest in meticulous compliance with the law by public officials"). *See also, e.g., O'Donnell Constr. Co. v. District of Columbia*, 963

F.2d 420, 429 (D.C. Cir. 1992); *Mova Pharm. Corp.*, 140 F.3d at 1066 (upholding preliminary injunction when district court concluded that the public's interest in the "faithful application of the laws" tipped public interest prong in favor of requested preliminary injunction); *Nobby Lobby, Inc. v. City of Dallas*, 970 F.2d 82, 93 (5th Cir. 1992) (approving district court conclusion that "the public interest always is served when public officials act within the bounds of the law and respect the rights of the citizens they serve").

In *Mova Pharm. Corp. v. Shalala*, 955 F. Supp. 128, 131 (D.D.C. 1997), this Court held that the faithful application of the Hatch-Waxman Act outweighs the public interest in a marginal increase in the availability of low-cost generic drugs. On appeal, the D.C. Circuit affirmed, holding that the public's interest in the availability of generic drugs does not outweigh its overriding interest in the faithful application of the laws by government officials. *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1066 (D.C. Cir. 1998). The public interest simply is not served by the capricious, precipitous approval of generic drugs, where questions remain about the processes and standards used to evaluate such products. The public interest favors an immediate remedy for Mutual's unwarranted exclusion from FDA's administrative review process.

III. PLAINTIFF – AND THE PATIENT POPULATION – WILL SUFFER IRREPARABLE INJURY ABSENT IMMEDIATE RELIEF.

Unless enjoined by this Court, FDA's conduct will cause substantial, imminent, and irreparable injury to patients and to Takeda, for multiple reasons.

First, FDA's actions pose a substantial and imminent harm to prospective patients who will be placed on Mitigare. As noted above, FDA stated in its response to Mutual's

2010 Citizen Petition 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." Ex. 1 at 3 (emphasis added). FDA also stated 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." *Id.* (emphasis added). In sharp contrast to this stated policy, which was based on FDA's own investigation and findings with regard to oral colchicine products, the label FDA recently approved for Mitigare lacked the information about low-dose treatment for acute gout and the drug-drug interaction dosing adjustments. Ex. 2.

Notably, before FDA approved Colcrys® and removed unapproved colchicine products from the market, the unapproved products generally contained labeling information that lacked such safety information. Verified Complaint ¶ 4; Exs. 3, 4. Labeled in this manner, these unapproved products were associated with a significant number of fatalities related to drug-drug interactions and colchicine toxicity. *Id.* Thus, reverting to a regime where colchicine products lack the requisite safety information would take patients back to an environment where they face a significantly higher risk of harm from colchicine toxicity than is necessary.[8] Hikma has already launched this

[8] Amplifying this risk is the fact that Mitigare is a capsule, rather than a tablet, like Colcrys®. Verified Complaint ¶ 55; Ex. 2 at 9. The reduced, safe dosing for drug-drug interactions contained in the Colcrys® labeling and the protease inhibitors labeling recommends 0.3 mg doses – in other words, *half* a Mitigare capsule. *Id.* Unlike Colcrys®, a scored tablet that can be easily split, capsules are more difficult to split precisely, which poses an added risk that an excess dosage could inadvertently be

ineffectually labeled colchicine product as a branded product and can laugh it as a generic product at any time. The threat to patients is imminent. Woods Decl. ¶¶ 3, 10, 30, 33.

Second, FDA's action also irreparably harmed Takeda. By failing to afford Takeda its procedural rights to protect its patent interests and file a Citizen Petition to challenge Hikma's application, FDA inflicted an irreparable harm on Takeda. *See Ctr. For Law & Educ. v. Dept. of Educ.*, 396 F.3d 1152, 1157 (D.C. Cir. 2005) (plaintiff may sue to enforce statutory procedural right designed to protect threatened concrete interests); *Fund for Animals v. Norton*, 281 F. Supp.2d 209, 222 (D.D.C. 2003) ("[W]hen combined with the irreparable aesthetic injuries alleged by plaintiffs, such procedural harm [for violating a procedure of the National Environmental Policy Act] does bolster plaintiffs' case for a preliminary injunction."); *Fund for Animals v. Clark*, 27 F. Supp.2d 8, 14 (D.D.C. 1998) (same). Under 20 C.F.R. § 10.30, any person or entity, including pharmaceutical companies, may file a citizen petition, asking FDA to refrain from taking an administrative action. But here, Takeda never had the opportunity. If FDA had complied with its governing regulations and statutory mandate, Takeda would have received notice of the pending application under the Hatch-Waxman Act. Now, absent immediate intervention from this Court, it is too late. For these reasons, Takeda suffered an irreparable procedural harm at the hands of FDA.

Third, FDA's approval of Mitigare authorized Hikma to launch the product in the market at any moment, and it in fact did so as a branded product on October 3, 2014.

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ingested resulting in toxicity or that an insufficient dosage could inadvertently be ingested resulting in a dosage that is not effective. Verified Complaint ¶ __. In fact, FDA has told consumers not to split capsules. Specifically, FDA stated that "some pills, such as capsules . . . should always be taken whole." Ex. 18, FDA For Consumers, "Tablet Splitting: A Risky Practice" (last updated December 7, 2013).

Woods Decl. ¶ 33. It intends to launch a generic version of Mitigare "imminently." *Id.*[9] The market impact on Takeda absent a stay would be so devastating as to constitute irreparable harm – and it is entirely unrecoverable. Within the first four weeks, the entry of a lower-cost colchicine drug product to the market would cause Takeda to lose between [redacted] of the number of Colcrys® prescriptions that would otherwise be written and filled; within the first twelve months, it would cause Takeda to lose [redacted] of these prescriptions. *Id.* ¶¶ 59-61; *see also id.* ¶¶ 45-49 (describing the automatic substitution of generic Mitigare for Colcrys® that will occur at pharmacies), ¶¶ 50-54 (describing the erosion of market share that generic Mitigare will cause to Colcrys® for patients enrolled in managed care plans), ¶ 55 (describing the erosion of market share that generic Mitigare will cause to Colcrys® for among patients who are uninsured or pay cash for prescription drugs), ¶¶ 56-57 (describing the erosion of market share that generic Mitigare will cause to Colcrys® for Medicaid funded prescriptions).

Among other things, the significant loss of revenue that would result from this immediate erosion of market share would irreparably harm Takeda's research and development efforts with respect to new drug products. *Id.* ¶ 23. In fiscal year 2014, Colcrys® is expected to account for [redacted] of Takeda's operating margin (profit before taxes) in the United States. Those profits are used to fund ongoing and new research programs to discover new medications and invested to support the marketing and promotion of newer brands. If Takeda were to lose access to these revenues and profits,

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[9] Generic manufacturers can flood the market within hours of obtaining final FDA approval. *See* Woods Decl. *See also* Stephanie Saul, "A Generic Drug Tale, With an Ending Yet to Be Written," N.Y. Times, C1 (Aug. 15, 2006); *In re Buspirone Patent Litig.*, 185 F. Supp. 2d 340, 346 (S.D.N.Y. 2002).

all of these important activities would be affected negatively, prolonging the conduct of clinical studies and/or eliminating our ability to fund certain programs to advance patient care. *Id.* ¶ 69. If West-Ward enters the market with a generic version of Mitigare, Takeda's profits will be significantly lower than they otherwise would have been for the reasons described above, and significantly fewer funds would be available for research and development than would be available if West-Ward's generic product does not enter the market. *Id.* ¶ 70. This is critically important because during fiscal year 2014, Takeda is in the midst of four concurrent product launches – treating diabetes, depression, irritable bowel syndrome, and obesity – which rely on income generated from Colcrys® to fuel investment in those new products. *Id.* ¶ 71. [redacted] *Id.* ¶ 72.

Because of several market forces specific to Colcrys®, the market impact just described would not be reversible if Mitigare is later taken off the market. *Id.* ¶¶ 63-68. Physicians and patients will turn to alternative treatment options, as they did when FDA ordered unapproved colchicine products removed from the market in 2010. *Id.* Takeda

has invested years of effort in attempting to recover from the significant negative press, negative feedback from key customers, and damage to key relationships that occurred at that time. *Id.* ¶ 64. Additionally, Takeda has expended hundreds of millions of dollars to develop, patent, and promote Colcrys®, and would lose the value of its investment if a generic single-ingredient oral colchicine product were permitted to prematurely enter the market. *Id.* ¶ 21.

It is well settled that these types of harm constitute irreparable harm sufficient to warrant a TRO. As this Court has explained, "It is not at all difficult to foresee that [a pioneer drug company's] market position would collapse as soon as one or more generic drugs became available. [The innovator] would lose its head start in the market and its continued viability would be at issue. It could never recoup from FDA any losses that would occur. . . . These are the kinds of circumstances in which irreparable harm has been found." *CollaGenex Pharms., Inc. v. Thompson*, No. 03-1405 (RMC), 2003 U.S. Dist. LEXIS 12523, at *32 (D.D.C. July 22, 2003) (citing cases); *see also In re Cardizem Antitrust Litig.*, 200 F.R.D. 326, 340-41 (E.D. Mich. 2001) (describing predictable pattern of pioneer market share loss of up to 90% upon entry of competing generics); *Sanofi-Synthelabo v. Apotex, Inc.*, 488 F. Supp. 2d 317, 342-44 (S.D.N.Y. 2006) (describing sequence of events whereby generic drugs erode market share of pioneer drugs and noting that "irreversible price erosion . . . is a legitimate basis for a finding of irreparable harm"), *aff'd*, 470 F.3d 1368 (Fed. Cir. 2006); *Merrill Lynch, Pierce, Fenner & Smith, Inc. v. Bradley*, 756 F.2d 1048, 1054 (4th Cir. 1985) (noting that "customers cannot be unsolicited").

Moreover, because the foregoing losses can never be recovered from FDA, Takeda will be irreparably harmed unless FDA's conduct is enjoined promptly. *See Clarke v. Office of Fed. Hous. Enterprise Oversight*, 355 F. Supp. 2d 56, 65-66 (D.D.C. 2004) (holding that economic losses constitute irreparable injury where they are unrecoverable due to government immunity); *Nat'l Med. Care, Inc. v. Shalala*, 1995 WL 465650, at *3 (D.D.C. June 6, 1995) ("[T]he policy considerations behind the judiciary's general reluctance to label economic injuries as 'irreparable' do not come into play in APA cases: even if the Plaintiffs ultimately prevail on the merits, they cannot bring an action to recover the costs of their compliance with the Defendant's unlawful retroactive rule, and thus will not be able to alleviate their economic damage through subsequent litigation."); *Woerner v. Small Bus. Admin.*, 739 F. Supp. 641, 650 (D.D.C. 1990) (finding irreparable injury where government is immune from damage suits to recover for economic losses); *Informatics Corp. v. United States*, 40 Fed. Cl. 508, 518 (1998) (finding irreparable harm where, absent the injunction, movant could recoup only the bid preparation costs and not lost profits).

Takeda also will suffer irreparable reputational harm absent entry of a temporary restraining order. Any injuries or fatalities resulting from the Mitigare label's lack of drug-drug interaction and low dosage safety information no doubt will unfairly be imputed to Colcrys® by the consuming public, which would lead to reputational harm for the product and possibly to Takeda. Verified Complaint ¶ 63. Patients are unlikely to draw distinctions between colchicine products or appreciate that safety risks attributable to one product's label are not applicable to the other seemingly similar product. Takeda also will suffer significant loss of goodwill and harm to the company reputation from the

perception that Takeda is causing a generic product to be taken off the market and thereby increasing costs for patients, prescribers, payers, and the overall health system. This will damage Takeda's corporate reputation, jeopardize key customer relationships, and generate significant negative publicity. Woods Decl. ¶ 66. *See also id.* ¶ 20 (discussing Takeda's significant promotional efforts and repair of goodwill since obtaining FDA approval). These adverse effects on business reputation, goodwill, and relationships with physicians and patients constitute irreparable harm sufficient to warrant injunctive relief. *Tate Access Floors v. Interface Architectural Res., Inc.*, 132 F. Supp. 2d 365, 378 (D. Md. 2001) (finding irreparable harm based in part on the "loss of long-term relationships with major customers, beyond the short-term loss of individual sales"); *aff'd*, 279 F.3d 1357 (Fed. Cir. 2002); *Patriot, Inc. v. Dep't of Hous. and Urban Dev.*, 963 F. Supp. 1, *5 (D.D.C. 1997) (asserting that damage to business reputation supports finding of irreparable harm).

IV. INJUNCTIVE RELIEF WILL NOT BURDEN DEFENDANTS' OR HIKMA'S INTERESTS.

Neither FDA nor Hikma can contend that it will be burdened if a TRO is issued because neither has any legitimate interest in engaging in action that is contrary to the FDCA or that jeopardizes patients' health and safety. Moreover, granting this motion would merely preserve the status quo by preventing Mitigare, a drug with known potential for life-threatening toxicity, from overtaking the market pending further consideration by this Court. *See Anderson v. Davila*, 125 F.3d 148 (3d Cir. 1997); *Dist. 50, United Mine Workers v. International Union, United Mine Workers*, 412 F.2d 165, 168 (D.C. Cir. 1969) ("The usual role of [an] injunction is to preserve the *status quo*.").

Nor would Hikma suffer any irreparable harm were the status quo preserved. At worst, entry of a TRO would delay Hikma's entry into the generic market, but for good reason – to enable appropriate review of FDA's decision to approve a generic that does not meet statutory standards for approval.

Preserving the status quo until the parties can be heard will result in no harm to FDA or Hikma. Any resulting burden is far outweighed by the risk to patients and Takeda if injunctive relief is denied and Hikma markets its product to unsuspecting patients with labeling that lacks critical details about drug-drug interactions and appropriate directions for dosing and dose adjustments.

CONCLUSION

Plaintiff's motion for a TRO and/or preliminary injunction should be granted.

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