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

REDACTED REPLY IN SUPPORT OF MOTION FOR TEMPORARY RESTRAINING ORDER OR PRELIMINARY INJUNCTION

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INTRODUCTION

Colcrys® is a single-ingredient colchicine drug. Mitigare is a single-ingredient colchicine drug. Colcrys® is indicated for, among other things, the prophylaxis of gout flares. Mitigare is indicated for the prophylaxis of gout flares. Colcrys®' labeling contains specific instructions for low-dose administration of the drug for gout flares, along with detailed instructions for administering the drug concomitantly with other products that may produce dangerous drug-drug interactions. FDA specifically said in a 2011 citizen petition response that, for safety reasons, similar language should appear on any single-ingredient colchicine drugs indicated for the prophylaxis of gout flares. Mitigare's labeling does not contain that language. The question in this case is whether FDA's approval of Mitigare with such labeling was reasonable. The answer is no.

The reasons behind Hikma's strenuous efforts to avoid referencing Colcrys® and its labeling are obvious: Hikma wanted to avoid subjecting itself to the patent litigation process mandated under the Hatch-Waxman Act, and to launch Mitigare ahead of other generic competitors who *did* follow the correct process. *See* D. Del. TRO Order, attached hereto as Exhibit A, at 7. But that provides no basis for FDA to go back on its previous mandates, to violate the statute, and to flout its own stated policies, all to approve this drug.

ARGUMENT

I. FDA's Approval of Mitigare is Arbitrary and Capricious Because The Agency Acted Contrary to Previous Determinations Without Sufficient Justification.

Mutual (Takeda's predecessor) conducted two separate sets of clinical studies to support the safety and efficacy of Colcrys®, each directed toward the goal of reducing colchicine toxicity and related fatalities. A.R. 1-27[1]; Verified Compl. Ex. 1. First, Mutual studied whether a low

[1] All pages of the Administrative Record cited herein are attached as Exhibit B.

colchicine dose could be effective to treat gout flares without the known side effects of the drug (a study called the "AGREE" trial). *Id.* at 6. Second, Mutual studied drug-drug interactions. *Id.* at 6-7. FDA recognized the scientific value of these studies in responding to Mutual's citizen petition in 2011 and in determining the requirements for the labels of Colcrys® and other single-ingredient colchicine drugs. *See id.*; Takeda Mem. 20-21. *Nothing* in the entire administrative record adequately explains why FDA has abandoned those requirements now. *See Friedman v. Sebelius*, 686 F.3d 813, 828 (D.C. Cir. 2013) (action arbitrary and capricious where agency "failed to explain its departure from the agency's own precedents"); *Fox v. Clinton*, 684 F.3d 67, 80 (D.C. Cir. 2012) (agency decision "arbitrary and capricious for want of reasoned decisionmaking").[2]

[2] Hikma has proffered declarations of several witnesses on factual and legal issues relating to the Mitigare application process. *See, e.g.*, Tsein and Todd Decls. Those declarations are not proper in an APA case, where the only inquiry is whether the agency's decision is supported by the administrative record. "[A] reviewing court 'should have before it neither more nor less information than did the agency when it made its decision.'" *Silver State Land, LLC v. Beaudreau*, 2014 WL 3670029, at *2-*3 (D.D.C. July 24, 2014) (citations omitted)*; Hill Dermaceuticals, Inc. v. Food & Drug Admin.*, 709 F.3d 44, 47 (D.C. Cir. 2013) (same) (citation omitted); *CTS Corp. v. E.P.A.*, 759 F.3d 52, 64 (D.C. Cir. 2014) (citing *Hill*).

Mr. Tsein's declaration should also be excluded because it consists of legal conclusions. *See Convertino v. U.S. Dep't of Justice*, 772 F. Supp. 2d 10, 12-14 (D.D.C. 2010). In his declaration, Mr. Tsein opines that "the 505(b)(2) application pathway was, under the facts of this case, an appropriate avenue through which Hikma could obtain FDA approval for Mitigare™." Tsein Decl. ¶ 13; *see also id.* ¶ 40. But "[a]n expert witness may not deliver legal conclusions on domestic law, for legal principles are outside the witness' area of expertise under Federal Rule of Evidence 702." *Weston v. Wash. Metro. Area Transit Auth.*, 78 F.3d 682, 684 n.4 (D.C. Cir. 1996). *See also Bank of New York v. Fed. Deposit Ins. Co.*, 453 F. Supp. 2d 82, 98-99 (D.D.C. 2006) (declining to consider expert's opinion about correct interpretation of regulatory scheme as "expert testimony on domestic law is not permitted"). Mr. Tsein's legal conclusion about the correct application of FDA's authority to the facts of the case "intrude[s] upon the duties of . . . the trier of fact." *Convertino*, 772 F. Supp. 2d at 12 (quotation omitted).

A. FDA Inexplicably Departed From Its Low-Dose Labeling Requirement For Acute Gout Flares.

FDA has failed to explain its abrupt departure from its own precedent relating to low-dose labeling. In its 2011 citizen petition response, FDA noted the risk of cumulative toxicity in patients who take colchicine for prophylaxis of gout flares and then take additional colchicine for acute gout flares. *See* A.R. 24; Verified Compl. Ex. 1. That observation makes common sense; patients already taking colchicine for prophylaxis of gout flares will already have existing levels of colchicine in their bodies before commencing colchicine treatment for an acute gout flare. If the two therapies—prophylaxis and treatment—are not coordinated, a risk of toxicity exists due to the therapies' cumulative effects. *See* A.R. 5.

Accordingly, FDA concluded in 2011 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."[3] A.R. 24; Verified Compl. Ex. 1 (emphasis added). Mitigare is just such a product—a single-ingredient colchicine product intended for use in prophylaxis of gout flares. But its labeling omits any information about the low-dose regimen for acute gout flares. *See* A.R. 138; Verified Compl. Ex. 2.

FDA does not defend Mitigare's omission of the low-dose information on the basis that the cumulative risk of toxicity no longer exists. Rather, the agency claims that "[b]ecause Mitigare is not indicated for treatment of acute gout flares that may occur during prophylaxis, its labeling appropriately does not describe a dosing regimen for this use." FDA Opp. 16.

[3] Hikma argues that FDA's statement addresses only a situation "where the applicant seeks approval for *both* prophylaxis of gout flares *and* treatment of acute gout flares." Hikma Opp. 20 (emphasis in original). But this mischaracterizes the petition response, which specifically addresses a product "seeking approval for prophylaxis."

To begin with, FDA's assertion that labeling for a product need not be concerned with risks raised by an unapproved use does not square with its own regulations, which specifically acknowledge that risk information related to common "off label uses" may be required in labeling. *See* 21 C.F.R. § 201.57(c)(6) (providing that "[a] specific warning relating to a use not provided for under the 'Indications and Usage' section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard").

But even more important, FDA *specifically determined* in this administrative record that "if Mitigare is being used for prophylaxis, it may be natural for the provider to use it for acute treatment as well." A.R. 724. On this point, at least, FDA is consistent. In its 2011 citizen petition response, FDA similarly determined that the low-dose information is necessary on a label for a colchicine product indicated for prophylaxis because patients taking colchicine for prophylaxis have breakthrough flares and take additional colchicine for those flares. FDA determined that the two treatments are so closely related that they cannot safely be separated. *See* A.R. 24; Verified Compl. Ex. 1 at 24. That is why Colcrys®' labeling provides specific information regarding patients taking the product for prophylaxis who also suffer a flare. *See id.* In light of FDA's consistent conclusion that a drug indicated for *prophylaxis* of gout flares can and will be used to treat *acute* gout flares, FDA's conclusory statement excusing the deficiencies in Mitigare's label is completely insufficient. *See Amerijet Int'l, Inc. v. Pistole*, 753 F.3d 1343, 1350 (D.C. Cir. 2014) (a "conclusory statement[] will not do; an agency's statement must be one of *reasoning*") (internal quotation omitted; emphasis in original); *Lone Mtn. Processing, Inc. v. Sec'y of Labor*, 709 F.3d 1161, 1164 (D.C. Cir. 2013) (abuse of discretion where agency failed to explain why certain reasoning applied in the past but not to the case at issue).

B. FDA Inexplicably Departed From Requiring Specific Dosage Information Tied To Proven Instances of Drug-Drug Interaction.

FDA also has failed to explain its abrupt departure from its own precedent relating to drug-drug interactions. Colchicine is a "narrow" therapeutic index drug, meaning that there is a narrow window between effective and toxic doses. Verified Compl. Ex. 4 at 2. Numerous people have died from the effects of the drug—including patients who were administered colchicine doses within the normal therapeutic range. Verified Compl. Ex. 3. Over half the colchicine fatalities through June 2007 that were not overdoses involved patients who were taking clarithromycin, a commonly prescribed antibiotic, along with colchicine. *Id.*

Among the drugs intensively assessed in its drug-drug interaction studies, Mutual specifically studied clarithromycin and established that the concomitant use of clarithromycin and colchicine can increase blood levels of colchicine by over 200%. Based on the clarithromycin study and Mutual's several other studies, "FDA conclude[d] there is a risk for severe drug interactions in certain patients treated with colchicine and concomitant P-gp or strong CYP3A4 inhibitors." Verified Compl. Ex. 3 at 2. To address those drug-drug interaction risks, the Colcrys® label includes a number of specific dose reductions to offset increased colchicine levels caused by the interaction. Those specific dosage instructions include both the actual drugs that were studied and were shown to have an interaction, such as clarithromycin, and drugs that were *not* studied but are in the same general class as the drugs that were.[4]

FDA considered the new information about specific dose adjustments so important that FDA issued a safety alert informing the public about the new dose adjustments and

[4] For example, clarithromycin is a strong CYP3A4 inhibitor, so FDA extrapolated the dose recommendations for clarithromycin to other strong CYP3A4 inhibitors: "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." Verified Compl. Ex. 6 at 4-5.

recommending that "Healthcare professionals refer to Colcrys' approved prescribing information for specific dosing recommendations and additional drug interaction information." Verified Compl. Ex. 3 at 1. And in its 2011 Citizen Petition response, FDA stated 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*." A.R. 3; Verified Compl. Ex. 1 at 3 (emphases added).

Mitigare is just such a product. But Mitigare's label contains no such "relevant dose adjustments needed to prevent unnecessary toxicity." Instead, its label reverts back to the pre-Colcrys® admonition that if use of colchicine with certain classes of drug is necessary, prescribers should reduce the daily dose to avoid drug-drug interactions. A.R. 138; Verified Compl. Ex. 2 at 2. FDA has not sufficiently justified its marked departure from what it required in 2011.

FDA's justification, such as it is, stems from some additional drug-drug interaction studies Hikma performed. FDA Opp. 17. To support Mitigare's approval—and specifically to avoid referencing Colcrys®, *see* A.R. 686—Hikma studied four different drugs in the same general class as the drugs studied by Mutual. These studies showed no significant drug-drug interactions relating to the four drugs Hikma chose. A.R. 670. From this, FDA concluded that Hikma's studies "raise questions about the generalizability of detailed dose modification recommendations to drugs that have not been directly studied." FDA Opp. 17. In other words, Hikma showed that *some* drugs in the relevant classes do not cause interactions, and therefore the results obtained by Mutual may not be generally applicable.

Based on FDA's conclusion that Mutual's results might not be generally applicable, it might have been appropriate to allow the Mitigare label to omit dosing adjustments for as-yet-

unstudied drugs. But that is not what FDA did. Instead, the agency permitted the Mitigare label to omit *all* of the Colcrys® dosing adjustments—including dosing adjustments for the drugs that Mutual actually studied and for which it had found a risk of dangerous interactions.

That conclusion is not defensible. Mutual's results for the drugs it studied are still very much valid. The dosing adjustment for clarithromycin, to take one example, is based on the specific blood level increase Mutual demonstrated with clarithromycin. There is no basis to allow Hikma to exclude the specific dosing recommendations for Mutual's studied drugs. And FDA offers no adequate explanation for allowing the Mitigare label to omit information regarding the drug-drug interactions that were actually characterized by Mutual. FDA's reasoning—that Hikma's additional studies showed no drug-drug interactions for four *other* drugs—"offers only a partial, and ultimately inadequate, explanation." *Communications and Control, Inc. v. FCC*, 374 F.3d 1329, 1336 (D.C. Cir. 2004).

The Mitigare label also omits other important drug-drug interaction information from Mutual's studies. The results of Mutual's studies, which are included in the Colcrys® label, show the specific amount of colchicine blood level increase for each drug that was studied. For example, the Colcrys® label notes that colchicine blood levels increased approximately 250% in the study with clarithromycin. Prescribers use those study results to make informed decisions regarding concomitant use of colchicine with certain classes of drug. But Mitigare's label contains no such information about the drugs Mutual studied. *See* 21 CFR. § 201.57(c)(13)(i)(C) (specifying that the pharmacokinetics section of prescription drug labeling "*must* describe the clinically significant pharmacokinetics of a drug", and that "[i]nformation regarding … drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics) … *must* be presented if

clinically significant) (emphasis added). FDA has not even attempted to explain why the Mitigare label omits Mutual's study results—other than its candid acknowledgment that Hikma specifically was attempting to avoid referencing Colcrys®. *See* A.R. 686. FDA's failure to explain why the Mitigare label need not disclose Mutual's study results—in direct contradiction of its earlier findings and public warnings—is arbitrary and capricious.

II. FDA's Approval of Mitigare Is Arbitrary and Capricious Because Mitigare Is Not Safe Under the Conditions Prescribed, Recommended, or Suggested in Mitigare's Label.

A new drug cannot be marketed unless FDA determines that it is 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). Mitigare's label glaringly omits clinically important data and guidance regarding [1] the low-dose regimen for acute gout flares and [2] the dose adjustment recommendations for certain drug-drug interactions (DDIs). Those labeling omissions are not based on the underlying science. They are based on Hikma's stated goal of circumventing any reference to Colcrys®. The deficient label resulting from Hikma's scientific and legal acrobatics renders Mitigare unsafe.

Before Colcrys® was approved, single-ingredient oral colchicine was marketed without any approved application, and it was associated with significant safety problems, including over 150 deaths through June 2007. Takeda Mem. at 7. Citing those safety issues, FDA took enforcement actions against the unapproved products and removed them from the market. Verified Compl. Ex. 4 at 3. When Mutual thereafter sought approval to make and market Colcrys®, Mutual supported its application with studies of methods designed to increase the safe use of colchicine. *See supra* at 2-3. Mutual's studies changed the paradigm regarding the use of colchicine to treat gout in two significant respects. First, based on Mutual's studies, FDA concluded that the low-dose regimen for acute gout flares must be included in the label for a

product indicated for prophylaxis (such as Mitigare). A.R. 24; Verified Compl. Ex. 1 at 24. Second, also based on Mutual's studies, FDA concluded that drug-drug interaction information, including dose adjustments, must be included in the labeling of any single-ingredient colchicine drug product (such as Mitigare). A.R. 21; Verified Compl. Ex. 1 at 19-20.

Despite Mutual's advancements and FDA's previous determinations, FDA now seeks to turn back the clock. Mitigare's labeling does not include any of the new information developed by Mutual and deemed worthy of an FDA public safety alert. The labeling omits the low-dose regimen for treating acute gout flares, and it omits specific dose adjustments needed to avoid potentially fatal drug-drug interactions. Takeda acknowledges that decisions regarding drug safety are typically within the FDA's expertise. But the circumstances of Mitigare's approval are egregious, and they evince a complete disregard for FDA's statutory and scientific obligations to ensure that drugs are safe and effective. Instead, the administrative record and history of Hikma's product show that the development of the Mitigare labeling was thoroughly driven by Hikma's stated desire to avoid referencing Colcrys®, not by safety concerns.

First, it is important to recall the history of this product. In 2010, on FDA's advice, Hikma (through West-Ward) submitted a 505(b)(2) application for a duplicate of Colcrys®. Hikma submitted a 505(b)(2) application—rather than an abbreviated new drug application (ANDA)—to avoid referencing Colcrys® and to circumvent Mutual's patents. Mutual's 2010 citizen petition reminded the agency that duplicate drugs should be submitted under ANDAs and not 505(b)(2) applications. FDA subsequently acknowledged and corrected its mistake, and West-Ward withdrew its 505(b)(2) application. It then made a slight change to the dosage form—from tablet to capsule—and *resubmitted* the product under a 505(b)(2) application.

In its second attempt to secure approval of a Colcrys® clone, and to avoid the Colcrys® information regarding severe drug-drug interactions, Hikma conducted its own drug-drug interaction studies on four drugs. Unlike Mutual, which had studied commonly co-administered drugs that were causing interactions and fatalities, Hikma cherry-picked its drugs specifically to avoid referencing Colcrys®. Even FDA candidly acknowledges as much in the administrative record, stating that "West-Ward purposely used this particular set of inhibitors to avoid any overlap in data with Colcrys" and that "West-Ward stated its intention to not rely on Colcrys as a listed drug or on published literature describing the studies of Colcrys." A.R. 701. Similarly, FDA noted that [redacted] (emphasis added).

The results of Hikma's scientific and legal acrobatics are evident in Mitigare's labeling. Similar to the old labeling for unapproved colchicine products, the Mitigare labeling does not include the Colcrys® low-dose regimen for acute gout flares. And similar to the old colchicine labeling, Mitigare's labeling contains merely a general precaution to reduce the dose and monitor the patient if colchicine is co-administered with certain other drugs. In other words, FDA essentially reverted back to the old, pre-Colcrys® regime that had resulted in unnecessary toxicity and deaths. As FDA has explained:

> 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.

A.R. 19; Verified Compl. Ex. 1 at 19. That stale admonition—avoid when possible, use caution when necessary, monitor for signs of toxicity—is now on Mitigare's label. FDA determined that such labeling was unsafe in 2011. *See id.* at 19-20. It is still unsafe now.

Hikma's desire to avoid referencing Colcrys®—and the resulting obligation to submit paragraph IV certifications to the numerous patents covering Colcrys®—is not surprising. But *FDA's* tolerance of Hikma's gymnastics is stunning. To intentionally ignore information that FDA previously had found would reduce unnecessary toxicity and fatalities is—to put it mildly—not in the interest of the public health.

III. FDA Violated Its Own Rules By Failing to Require Hikma to Reference Colcrys® In Its Application.

All of the parties agree that if Hikma had referenced Colcrys® as the listed drug in its 505(b)(2) application, Hikma would have been required to file certifications to each of the relevant Colcrys® patents listed in the Orange Book and to notify Takeda if it was providing a Paragraph IV certification. Takeda Mem. 28; FDA Opp. 18; Hikma Opp. 23. All of the parties similarly agree that had Hikma referenced Colcrys®, Takeda would then have been able to file a patent infringement lawsuit, resulting in a 30-month stay of Hikma's application while that patent suit was litigated.[5] *See* Takeda Mem. 28-29; FDA Opp. 18; Hikma Opp. 23. The only dispute between the parties appears to be whether it was arbitrary and capricious for FDA to permit Hikma to proceed without referencing Colcrys® as the listed drug in its application. It was, for two reasons that neither FDA nor Hikma refute.

First, FDA's policy is that a 505(b)(2) applicant must choose the "most appropriate" listed drug to be its reference listed drug. That standard was not applied here. Second, FDA's

[5] Indeed, this is precisely what three other companies did, and those parties and Takeda are in the midst of patent litigation in Delaware.

procedural requirements make clear that an applicant must reference another product if FDA relies on studies or data relating to that product in approving the applicant's application. Verified Compl. Ex. 11 at 7-8. That standard also was not applied here.

A. Colcrys® Was the Most Appropriate Drug for Hikma to Reference.

FDA has directed that 505(b)(2) applicants must choose the "most appropriate" listed drug to be its reference listed drug. Reckitt Citizen Petition Response, attached hereto as Exhibit C, at 8 (instructing that a "505(b)(2) applicant should determine which listed drug(s) is most appropriate for its development program"). But instead of choosing the *only* single-ingredient oral colchicine product in 0.6 mg strength on the market, Hikma picked a much older combination product that includes a different strength of colchicine along with another drug. It did not make that selection based on science, or on the public health, or on the similarity of its product with that old combination. It made that selection to circumvent the need to certify to the Colcrys® patents. *See, e.g.*, A.R. 686 (describing Hikma's efforts "to avoid potential patent issues" with Colcrys®); [redacted] Despite their combined 55 pages of briefing, neither FDA nor Hikma has offered any explanation as to why Col-Probenecid was more similar or more appropriate for Hikma to cite than Colcrys®—and they have certainly not pointed to anything in the administrative record that would support such a conclusion.

Nor could they. Colcrys® is the drug that is "most appropriate" for Mitigare's development program. Both Colcrys® and Mitigare are single-ingredient oral colchicine products in 0.6 mg strength. Verified Compl. Ex. 5; A.R. 138. The only arguably material difference between the products is that Mitigare is a capsule and Colcrys® is a tablet. FDA itself describes Mitigare as "a similar single-ingredient colchicine product seeking approval for one of

the same indications as Colcrys (i.e., prophylaxis of gout flares)." A.R. 815. [redacted] Col-Probenecid, in contrast, differs in multiple ways from Mitigare—it involves both a different strength of the drug (0.5 mg of colchicine instead of 0.6 mg) and a formulation that combines that lower strength with another drug product, 500 mg of probenecid. A.R. 88.[6] It also has a different dosage form that Mitigare. And Col-Probenecid's labeling is much different than Mitigare's, which has labeling very similar to Colcrys®—except for the missing safety information. *See* Col-Probenecid label, attached hereto as Exhibit D. Given these facts, it is unsurprising that the Administrative Record is replete with discussions of and analyses comparing Colcrys® and Mitigare, without any similar discussions of Col-Probenecid. *See infra* at 15-17.

These facts strongly support Takeda's argument that FDA acted arbitrarily and capriciously by failing to require Hikma to reference Colcrys® in its application or certify to the Colcrys® patents. Hikma's response is nothing more than the circular argument that Hikma was not required to reference Colcrys® because FDA did not require it to do so. Hikma Opp. 25 ("In sum, FDA told Hikma that there was no need to certify to the patents listed for Colcrys®."). But that is the very question: whether FDA's failure to do so was arbitrary and capricious.

FDA's response fares no better. The agency argues that it determined that Mitigare was safe and effective "without relying on Colcrys®." FDA Opp. 18. That assertion is belied by the

[6] Hikma and FDA suggest that because Mutual relied on Col-Probenecid when seeking approval for Colcrys, Hikma could too. But when Mutual was seeking approval of Colcrys®, no approved single ingredient colchicine product was available, so Col-Probenecid was the most similar and most appropriate drug for Mutual to have referenced. That was no longer true by the time Hikma submitted its Mitigare application.

Administrative Record—which FDA produced on October 16, 2014 and was therefore not available at the time Takeda filed its opening brief. As we next explain, the proceedings before the agency make abundantly clear that FDA explicitly referenced and relied on the Colcrys® data—over and over and over again—in approving Mitigare.

Because the stated desire to avoid another party's patents is not a reasonable basis for failing to cite the "most appropriate" reference drug as required by FDA's own policies, FDA's action here was arbitrary and capricious.

B. FDA Improperly Relied on Colcrys® Data Even Though It Was Not a Referenced Drug.

FDA has made it clear that a 505(b)(2) applicant must reference another product if the agency relies on studies or data relating to that product in approving the applicant's application. Verified Compl. Ex. 11 at 1 (explaining that section 505(b)(2) "expressly permits FDA to rely, for approval of an NDA, on data not developed by the applicant" but directing that in such circumstances the applicant must cite the studied product). And the recently-produced Administrative Record makes it clear that FDA repeatedly and explicitly relied upon the Colcrys® data in approving Mitigare. *See*, *e.g.*, [redacted] A.R. 462 (FDA identifies the publication that

summarizes Mutual's studies as the third "literature reference" for drug-drug interaction information for colchicine). FDA also relied on the approved Colcrys® dosing for Familial Mediterranean Fever (FMF) to conclude that Hikma's proposed dosing for prophylaxis would not be expected to produce serious toxicity in patients with renal or hepatic impairment. A.R. 112. As FDA explained:

> Regarding dose-modifications due to renal or hepatic impairment, the review team concluded that the utility of the applicant's proposed dose adjustments was questionable given the dose range of colchicine for the prophylactic gout indication (i.e., 0.6-1.2 mg daily), which is already *less than or equal to half of the maximum dose of colchicine approved for chronic administration (Colcrys, FMF indication), and thus would not be expected to produce serious toxicity, even if renal or hepatic impairment effectively doubled the concentration*.

Id. (emphasis added).

In analyzing drug-drug interaction concerns, FDA noted: "West-Ward *and Mutual's* DDI data *combined* suggests that P-gp inhibition may play a more dominant role than CYP3A4 inhibition." A.R. 701 (emphasis added). And FDA briefing documents include tables comparing Mitigare's drug-drug interaction data [redacted] to Colcrys® data and labeling. A.R. 688, 692, [redacted] In addition, FDA relied on Colcrys® drug-drug interaction data and labeling to reject Hikma's initial proposed labeling regarding drug-drug interactions. As FDA explained: "we are concerned that disparate recommendations in the labeling for Colcrys® (colchicine) and the proposed labeling for your product (a similar single-ingredient colchicine product seeking approval for one of the same indications as Colcrys® (i.e., prophylaxis of gout flares)) may cause patient and prescriber confusion with respect to drug-drug interactions." A.R.

815.[7] Ultimately, FDA determined that the Mitigare drug-drug interaction studies do not contradict the Colcrys® studies because the studies concerned different drugs. Based on that conclusion, the FDA "panel recommended that the West-Ward DDI studies should be included in labeling with the caveat that these results may not apply to other drugs that have not been studied." A.R. 672.

In fact, Mitigare's labeling would make no sense without the Colcrys® studies. The recommendation in Mitigare's labeling to avoid specified drug-drug interactions (*see, e.g.*, instructions to avoid concomitant use of Mitigare with inhibitors CYP-3A4 or P-gylcoprotein, and if avoidance is not possible, then reduced daily doses should be considered and patients should be monitored, A.R. 138-41 and Verified Compl. Ex. 2 at 1, 3-4) finds no support in—indeed, is inconsistent with—Hikma's own study results for Mitigare, which did not find any significant drug-drug interactions. A.R. at 48. The Mitigare labeling *is* consistent, however, with Mutual's studies of Colcrys®, which found significant drug-drug interactions. The only difference is that the Colcrys® labeling actually provides guidance for prescribers to safely and effectively reduce the dosage amounts, while the Mitigare labeling does not.

FDA also has indirectly relied on Colcrys® to promote Mitigare's safe and effective use, despite Mitigare's deficient label. When FDA approved Colcrys® in 2009, FDA issued an alert educating the public regarding the new dosage adjustments to reduce the risk of drug-drug interactions and referring healthcare providers to the Colcrys® label for specific dose adjustments. Verified Compl. Ex. 3. In particular, FDA recommended that "Healthcare

[7] FDA also rejected the first two names Hikma proposed for its product because the names were too similar to Colcrys and likely to cause confusion, given the names included "the identical beginning letter string, 'Col'," had "downstroke letters" in similar positions, and "share the same overlapping characteristics including, dose, route of administration, frequency of administration, strength, and indication." A.R. 647.

professionals refer to Colcrys®' approved prescribing information for specific dosing recommendations and additional drug interaction information." *Id.* at 1. That public and professional reliance has manifested itself in the years since then. Indeed, the American College of Rheumatology adopted the Colcrys® dosing and dose adjustments in its 2012 Guidelines for the Management of Gout, which state:

> For more specific prescriptive guidance, practitioners should consult the FDA-approved [Colcrys®] drug labeling, including … colchicine dose reduction (or avoidance of colchicine use) with drug interactions with moderate to high potency inhibitors of cytochrome P450 3A4 and of P-glycoprotein; major colchicine drug interactions include those with clarithromycin, erythromycin, cyclosporine, and disulfiram.

Ex. E at 1453. In considering safety issues for Mitigare, then, FDA inherently relied on the fact that patients and prescribers have been and continue to be exposed to the specific dosing adjustments associated with Colcrys®.

All of these examples, and many others like them, demonstrate that it was arbitrary and capricious to permit Hikma to avoid referencing Colcrys® out of a desire to circumvent certifying to the Colcrys® patents. FDA relied throughout the administrative record on the Colcrys® studies in conjunction with the Mitigare data to determine appropriate labeling language for the safe use of Mitigare. FDA therefore was required to ensure that Colcrys® was properly referenced before approving Hikma's application. Its failure to do so was arbitrary, capricious, and an abuse of discretion.

IV. Takeda Has Shown Irreparable Harm.

Hikma admitted during discussions regarding scheduling of a TRO hearing that the colchicine market is about to be flooded with a generic version of its drug Mitigare—and that once the drug enters the marketplace, Hikma will be unable (or at least unwilling) to take steps to

pull it back. As a result, nothing short of a judicial decision suspending or vacating FDA's approval of the drug can avoid the irreparable harm that is about to befall Takeda.[8]

Neither FDA's nor Hikma's arguments undercut Takeda's initial demonstration of irreparable harm. As a preliminary matter, FDA's reliance on Judge Kavanaugh's *concurring* opinion stating that some lesser showing of irreparable harm could not be offset by a strong likelihood of success on the merits, FDA Opp. 19, is misplaced. This Circuit continues to "appl[y] a sliding scale approach in evaluating the preliminary injunction factors. Under this analysis, if the movant makes an unusually strong showing on one of the factors, then it does not necessarily have to make as strong a showing on another factor." *ConverDyn v. Moniz*, 2014 WL 4477555, at *8 (D.D.C. Sept. 12, 2014) (internal quotations omitted) (citing and quoting *Davis v. Pension Benefit Guar. Corp.*, 571 F.3d 1288, 1291-92 (D.C. Cir. 2009)); *Sierra Club v. U.S. Army Corps of Engineers*, 990 F. Supp. 2d 9, 24 n.12 (D.D.C. 2013) (Jackson, J.) ("[I]n the absence of a precedential ruling [that *Winter* overruled the sliding-scale approach], this Court will apply the more lenient sliding scale standard to the injunction at issue here."); *Am. Meat Institute v. U.S. Dep't of Agriculture*, 968 F. Supp. 2d 38, 46 n.9 (D.D.C. 2013) (Jackson, J.) ("The D.C. Circuit has not yet held that the sliding scale analysis is no longer applicable; therefore, this Court will apply that standard to the injunction at issue here."). In any event, the injury Takeda will sustain if FDA's action remains unchecked is substantial and grave.

First, by depriving Takeda of its procedural rights to (i) protect its patent interests by filing a patent infringement lawsuit in district court; and (ii) protect its regulatory interests by

[8] Suspension or vacatur of FDA's approval decision would immediately render the drug an "unapproved drug," which would make it unlawful for pharmacists and others to move the product through interstate commerce. *See* 21 U.S.C. § 355(a) ("No person shall introduce . . . into interstate commerce any new drug unless an approval of an application . . . is *effective* with respect to such drug." (emphasis added)); *Doe v. Sullivan*, 938 F.2d 1370, 1372 (D.C. Cir. 1991) ("The FDC Act generally prohibits the use of unapproved drugs.").

filing a Citizen Petition with FDA under 21 C.F.R. § 10.30, FDA inflicted an irreparable procedural harm on Takeda. *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."). FDA entirely fails to address this point. And Hikma suggests—without citing support—that a procedural harm may not be "cognizable." Hikma Opp. 26. The case law in this Circuit holds otherwise. *See Norton*, 281 F. Supp. 2d at 222; *Fund for Animals v. Clark*, 27 F. Supp. 2d 8, 14 (D.D.C. 1998).

Hikma also argues that issuing a preliminary injunction to allow Takeda to file a Citizen Petition would serve no purpose because this Court will either (1) defer to FDA or (2) vacate FDA approval and require Hikma to certify to Colcrys®, which would negate the need for a Citizen Petition. Hikma Opp. 26. This argument, however, is misleading. Because Takeda was denied the opportunity to submit a Citizen Petition in this matter, the Administrative Record is lacking much of the information that Takeda would have put before FDA in connection with such a Citizen Petition. If this Court were to decide that FDA did not act arbitrarily and capriciously based on the Administrative Record currently before the Court, that decision very well could be faulty because the Administrative Record itself is incomplete. Takeda should not be deprived of its right to participate in the administrative process before FDA.

Second, Defendants' arguments contesting the severe harm Takeda will sustain to its business operations immediately upon entry of Hikma's unlawful drug into the marketplace also miss the mark. Takeda's expectation that it will lose [redacted] of its operating margin in the United States is not a minimal financial loss, and that loss is only expected to get worse over time. Indeed, Hikma's imminent launch not only endangers Takeda's profits but also its other

imperative United States business operations. *See* Woods Decl. ¶ 69. Hikma's unlawful entry into the marketplace also would [redacted] Takeda's research and development budget, disrupting promising research into innovative medicines. *Id.* ¶¶ 70, 72. And the loss of [redacted] of Takeda's operating income in the United States would require [redacted]. *Id.* ¶ 72. These types of structural corporate changes rise to the level of irreparable harm.[9] *See* [redacted]

Third, Takeda's claims about injuries to its reputation and good will are not "speculative," as FDA asserts. FDA Opp. 20. FDA admits that Takeda's claims are based "upon

[9] FDA argues that this percentage should be considered by examining Takeda's international parent corporation—a non-party to this suit. FDA Opp. 23–24. But FDA cites no authority for the notion that harm to the independent domestic entity—the party to the lawsuit—can be properly analyzed through the lens of its non-party international parent. Rather, the Court should consider exclusively whether Takeda USA will be severely hampered by Hikma's entry into the market, irrespective of the effects on its corporate parent. *See Serono Labs, Inc.*, 974 F. Supp. at 35 (finding irreparable harm by analyzing the financials of Serono Labs, a U.S. subsidiary of an international parent company).

what happened when other colchicine products were taken off the market years ago." *Id.* FDA offers no reason to believe the market for colchicine has changed materially since then.

Fourth, because Takeda's economic losses can never be recovered from FDA, injunctive relief is necessary to prevent Takeda from irreparable harm. This Court has long recognized that economic losses constitute irreparable injury where the plaintiff cannot recover for them due to government immunity. *See Clarke v. Office of Fed. Hous. Enterprise Oversight*, 355 F. Supp. 2d 56, 65-66 (D.D.C. 2004); *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). Because in this case there is no "possibility that adequate compensatory or other corrective relief will be available at a later date," preliminary injunctive relief is appropriate here. *Chaplaincy of Full Gospel Churches v. England*, 454 F.3d 290, 298 (D.C. Cir. 2006); *see also Hoffman-LaRoche, Inc. v. Califano*, 453 F. Supp. 900, 903 (D.D.C. 1978) (when no "adequate compensatory or other corrective relief will be available at a later date," the threat of economic losses warrants preliminary injunctive relief); *Am. Fed'n of Gov't Emps. v. United States*, 104 F. Supp. 2d 58, 76 (D.D.C. 2000) (finding irreparable harm where, absent injunction, movants could not recoup pay and benefits).

Both FDA and Hikma acknowledge that the absence of other available remedies typically justifies injunctive relief, but they contend the likely harm to Takeda is not serious enough. FDA Opp. 24; Hikma Opp. 27. However, several judges in this Court have held that "where, as here, the plaintiff in question cannot recover damages from the defendant due to the defendant's sovereign immunity, any loss of income suffered by a plaintiff is irreparable *per se*." *Feinerman v. Bernardi*, 558 F. Supp. 2d 36, 51 (D.D.C. 2008) (internal citations omitted); *see also Nalco Co. v. EPA*, 786 F. Supp. 2d 177, 188 (D.D.C. 2011); *Smoking Everywhere, Inc. v. FDA*, 680 F. Supp. 2d 62, 77 n.19 (D.D.C. 2010); *Alf v. Donley*, 666 F. Supp. 2d 60, 70 (D.D.C. 2009)). But even accepting that Takeda must show the harm it faces to be "serious" or "great," the potential harm to Takeda is both imminent and extremely serious, for the reasons discussed above. In short, absent immediate judicial relief, Takeda will suffer grave, and irreparable, harm.

V. The Public Interest Strongly Favors The Requested Relief.

The public interest plainly favors granting an injunction here. First and foremost, FDA is risking patients' health and safety by approving Mitigare without what FDA previously determined was necessary safety information. The label for Mitigare lacks the information about low-dose treatment for acute gout and the drug-drug interaction dosing adjustments. A.R. 138-46; Verified Compl. Ex. 2. Unapproved colchicine products prior to Colcrys®—which also lacked this safety information—were associated with a significant number of fatalities related to drug-drug interactions and colchicine toxicity. And as discussed above, none of the information relied upon by FDA or Hikma in the approval process for Mitigare contradicts or undermines FDA's earlier findings regarding the risks associated with higher-dose treatments and drug-drug interactions. *See supra* at 5-8. The need plainly still exists for such safety information, and by approving the Mitigare label without it, FDA has put the public at imminent risk.

Hikma contends that the public will be harmed by keeping its lower-cost product off the market. Hikma Opp. 29.[10] But the public does not benefit from drugs that, even though potentially lower in price, can cause serious—even life-threatening—medical risks without proper safety information. Patient health and safety are of paramount importance, and injunctive relief in this case will ensure that they are properly protected.

VI. Injunctive Relief Will Not Burden FDA's Or Hikma's Legitimate Interests.

Neither FDA nor Hikma argue that the agency will be harmed by issuance of preliminary injunctive relief in this case. Nor could they. Everyone stands to gain by ensuring that the laws are faithfully executed and that FDA abides by its statutory mandate. *See Fund for Animals, Inc. v. Espy*, 814 F. Supp. 142, 152 (D.D.C. 1993).

Hikma, for its part, argues that it faces greater harm than Takeda if the Court were to grant injunctive relief. Hikma Opp. 28. That argument is meritless. First, despite asserting that Takeda's inevitable and profound economic losses are insufficient for purposes of injunctive relief, Hikma relies on similar types of losses in arguing that the hardships weigh in its favor. *Id.* But unlike Takeda, none of the declarations Hikma cites provide hard numbers—or even projections—as to how much Hikma anticipates losing if it is temporarily prevented from selling Mitigare. *Id.* Takeda *has* provided such evidence, and it shows that Takeda stands to suffer substantial losses. Takeda Mem. 33-34.

[10] Troubling evidence in the Administrative Record indicates that FDA may have taken cost considerations into account in approving Mitigare. *See, e.g.*, A.R. 707 (noting as a "consideration for possible next steps" that "alternatives to Colcrys are being strongly called for"). Indeed, the agency went so far as to note the public's "need to have alternative colchicine products available" as a listed "con" to requiring additional drug-drug interaction studies from Hikma *despite additional studies being "scientifically justified*." A.R. 708. That consideration is completely improper on the agency's part. FDA's job is to ensure safety and efficacy of all drug products entering the market in the United States.

Second, Takeda did not unduly delay in seeking preliminary relief from the Court. Hikma Opp. 28. FDA and Hikma have apparently been in intense discussions regarding Mitigare's approval for years. Takeda was shut out of that process. It did not learn of the drug's approval until the afternoon of September 30, through a Hikma press release. Takeda Mem. 1 n.1. Takeda's counsel contacted FDA within days in an attempt to resolve the matter without need for judicial intervention. Stetson Decl., D.E. 3-5 ¶ 2. When those efforts were unsuccessful, Takeda filed this action the very next business day. This can hardly be seen as undue delay in seeking redress from the Court. By comparison, the cases Hikma cites for its "undue delay" argument involve circumstances where a plaintiff had delayed for weeks or months before seeking redress. *See Newdow v. Bush*, 355 F. Supp. 2d 265, 292 (D.D.C. 2005) (more than one month); *Open Top Sightseeing USA v. Mr. Sightseeing, LLC*, --- F. Supp. 2d ---, 2014 WL 2758603, at *3 (D.D.C. June 18, 2014) (request to delay preliminary injunction hearing by at least two weeks).[11]

In any event, any "harm" Hikma might suffer resulting from a delay of Mitigare's approval pending compliance with the proper procedures is a problem of Hikma's (and FDA's) own making. Several other generic colchicine applicants followed proper FDA procedures, certified to the Colcrys® patents, and now are engaged in patent litigation with Takeda in Delaware. *See supra* at 12 n.4. Hikma sidestepped that entire process by bending science and logic to avoid referencing Colcrys® in its application for Mitigare. If anyone is to blame for any delay that may result in distributing Mitigare, it is Hikma and FDA—not Takeda.

[11] Hikma's citation of *Open Top Sightseeing* is especially perplexing. That case stands for the proposition that denial of preliminary relief is warranted "where the party seeking an injunction had knowledge of the pending nature of the alleged irreparable harm." Hikma Opp. 28. Takeda had no knowledge that FDA was considering approval of Mitigare.

Finally, contrary to Hikma's assertions, Hikma Opp. 28-29, a preliminary injunction in this case will indeed preserve the status quo. While it appears Hikma tried to flood the market with its approved generic product immediately *after* learning of Takeda's two parallel requests for temporary relief, *see* Suppl. Woods Decl. ¶¶ 3-4, the judge in the Delaware patent case promptly issued a TRO ordering Hikma, among other things, to reach out to its customers and claw back any distribution of the product. Ex. A at 7 n.6. Hikma has since voluntarily agreed to extend that Order until at least October 31. Hikma Opp. 16. Thus, by its own agreement, Hikma is not currently marketing or selling Mitigare, and it will not be harmed if this Court were to issue preliminary injunctive relief maintaining this status quo.

CONCLUSION

For the foregoing reasons, and those in Takeda's opening memorandum, its motion for a temporary restraining order or a preliminary injunction should be granted.

Respectfully submitted,

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