UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

TAKEDA PHARMACEUTICALS U.S.A., INC., Plaintiff, v. SYLVIA BURWELL, Secretary of Health and Human Services, *et al*., Defendants.	)	Civil Action No. 14-1668 (KBJ)

DEFENDANTS' OPPOSITION TO PLAINTIFF'S MOTION FOR A TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION

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INTRODUCTION

Takeda Pharmaceuticals U.S.A., Inc. ("Takeda") filed this suit in an effort to maintain its monopoly with its colchicine product, Colcrys, a drug used to treat gout.[1] Despite the fact that West-Ward Pharmaceutical Corp. ("West-Ward")[2] obtained approval of its colchicine product (Mitigare) via the same statutory pathway as Takeda,[3] relying on the same previously-approved product, Takeda claims that FDA's approval of Mitigare was unlawful because the agency did not require Mitigare to use the same labeling as Colcrys. And despite having no knowledge of the scientific evidence underlying FDA's approval decision, Takeda baldly asserts that the failure to require identical labeling renders Mitigare unsafe and urges the Court to second-guess the agency's scientific judgment in that regard. Courts have unequivocally held, however, that the scientific determinations underlying the approval of a drug product fall squarely within the expert discretion of the FDA, which Congress has determined is in the best position to make such highly technical decisions.[4]

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[1] Colchicine products have been used for the treatment of gout for over 80 years. Colcrys was approved in 2009 for both the prophylactic treatment of gout and treating acute gout flareups, as well as familial Mediterranean fever ("FMF").

[2] West-Ward is the U.S. agent for Hikma International Pharmaceuticals LLC.

[3] The Colcrys New Drug Applications were originally owned by Mutual Pharmaceutical Company Inc. ("Mutual").

[4] *See, e.g., Serono Labs., Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998); *Schering Corp. v. FDA*, 51 F.3d 390 (3d Cir. 1995); *ViroPharma, Inc. v. Hamburg*, 898 F Supp.2d 1 (D.D.C. 2012); *Sanofi-Aventis U.S. LLC v. FDA*, 842 F. Supp.2d 195 (D.D.C. 2012); *Graceway Pharms., LLC v. Sebelius*, 783 F. Supp. 2d 104 (D.D.C. 2011); *Valeant Pharms. Int'l v. Sebelius*, No. 08-0449 (C.D. Cal. Sept. 14, 2009); *Astellas Pharma U.S., Inc. v. FDA*, 642 F. Supp. 2d 10 (D.D.C. 2009); *Biovail Corp. v. FDA*, 519 F. Supp. 2d 39 (D.D.C. 2007); *Glaxo Group, Ltd. v. Leavitt*, No. 06-469, 2006 U.S. Dist. LEXIS 10938 (D. Md. Mar. 6, 2006); *Somerset Pharms., Inc. v. Shalala*, 973 F. Supp. 443 (D. Del. 1997); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212 (D.D.C. 1996); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994); *Schering Corp. v. Sullivan*, 782 F. Supp. 645 (D.D.C. 1992), *vacated as moot sub nom. Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993).

Because Mitigare is *not* a duplicate of Colcrys, West-Ward was not required to have the same labeling as Colcrys or reference Colcrys. *See, e.g.,* Administrative Record ("AR") at 108 (attached as Exhibit A). The Colcrys labeling contains a 2-page table of dose modifications intended to help mitigate the risk of colchicine toxicity for patients taking Colcrys in combination with the drug products listed in the table. Compl. Ex. 5 at 5-6. The Mitigare labeling does not contain the same level of detail regarding dose modifications for patients taking colchicine for prophylaxis of gout flairs, but instead warns that patients taking certain drugs in combination with Mitigare should adjust the dose of Mitigare by "either reducing the daily dose or reducing the dose frequency, and the patient should be monitored carefully for colchicine toxicity." Compl. Ex. 2 at 4. FDA concluded that Mitigare is safe and effective for its intended use with this labeling, based on the data and information that West-Ward submitted to FDA to support its new drug application ("NDA"). *See*, *e.g.*, AR at122 (attached as Exhibit B). Indeed, in its review of the Mitigare application, FDA noted, "it may not be appropriate to recommend precise dose modifications based on currently available drug-drug interaction information for colchicine." AR at 120.

Takeda's unfounded claim that Mitigare is unsafe as labeled because its labeling differs from that of Colcrys is based on mere speculation and is belied by the substantial scientific evidence on which FDA relied in approving Mitigare. At bottom, Takeda is unhappy that it was unable to block the agency's approval of Mitigare. But Takeda's desire to preserve its colchicine marketing dominance provides no basis for overturning FDA's well-considered scientific decisionmaking, and this Court should decline Takeda's invitation to override the agency's expert judgment in evaluating the safety and effectiveness of drugs.

Takeda's claim that FDA denied Takeda its "rights to participate in the administrative

process" similarly lacks merit. *See* Memo. Of Points & Authorities In Supp. of Pl.'s Confidential Motion For A Temporary Restraining Order And/Or Preliminary Injunction ("Takeda Br.") at 1. Takeda has no "right" to participate in the approval process for another company's product and Takeda's papers are strikingly silent on the source of authority for this purported "right."

Because Takeda wholly failed to demonstrate a likelihood of success on the merits, its request for a preliminary injunction ("PI") can be denied without considering the remaining factors of the PI standard. However, Takeda has also failed to show that it would suffer irreparable harm in the absence of preliminary relief. Takeda is part of a large global corporation with annual revenue exceeding $15 billion dollars. Sales of Colcrys account for a mere 3% of that total. *See infra* at 23. Even if Takeda were to lose some portion of those sales due to a competitor entering the market, that loss falls far short of the irreparable harm necessary to support the relief Takeda has requested.

In addition, the harm West-Ward would suffer were this Court to grant Takeda's request and order FDA to suspend West-Ward's approval would likely equal, or exceed, that alleged by Takeda, rendering the balance of harms between the two companies equal. Nor would the public be served by disturbing FDA's considered scientific judgment – and its approval of a safe and effective drug – based on nothing more than the speculative assertions of a company seeking to foreclose economic competition. Takeda has thus failed to demonstrate that it can satisfy the balance of harms and public interest prongs of the PI standard. Because Takeda cannot satisfy any of the four elements necessary to support entry of emergency relief, this Court should deny Takeda's motion.

STATUTORY AND REGULATORY BACKGROUND

I. NEW DRUG APPLICATIONS

Under the Federal Food, Drug, and Cosmetic Act ("FDCA"), pharmaceutical companies seeking to market "pioneer" or "innovator" drugs must first obtain FDA approval by filing a new drug application ("NDA") containing extensive scientific data demonstrating the safety and effectiveness of the drug. 21 U.S.C. § 355(a), (b). The NDA must include the patent number and expiration date for any patent that claims the drug, or a method of using the drug, and for which a claim of patent infringement could reasonably be asserted against an unauthorized party. 21 U.S.C. § 355(b)(1), (c)(2). FDA must publish the patent information it receives, and does so in "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"). *Id.*; *see also* 21 C.F.R. § 314.53(e).

II. ABBREVIATED DRUG APPROVALS

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the "Hatch-Waxman Amendments") codified sections 505(b)(2) and 505(j) of the FDCA. 21 U.S.C. § 355(b)(2), (j). The Hatch-Waxman Amendments were intended to balance encouraging innovation in the development of new drugs with accelerating the availability to consumers of lower cost alternatives to such drugs. *See* H.R. Rep. No. 98-857 (Part I), 98th Cong., 2d Sess. at 14-15 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647-48; *see also, e.g., Tri-Bio Labs., Inc. v. United States*, 836 F.2d 135, 139 (3d Cir. 1987).

The FDCA permits an applicant to submit an abbreviated new drug application ("ANDA") seeking approval for a generic version of a previously approved drug product (a

"duplicate").[5] 21 U.S.C. § 355(j). ANDA applicants need not repeat the extensive clinical and nonclinical investigations to demonstrate the safety and efficacy of the generic product, as is necessary with an NDA. Rather, an ANDA relies on FDA's previous findings that the drug product approved under the NDA is safe and effective, and the FDCA sets forth in detail the information an ANDA must contain to meet the requirements for approval. *See* 21 U.S.C. § 355(j)(2)(A).

The FDCA, 21 U.S.C. § 355(b)(2), describes an application (a "505(b)(2) application") that contains full reports of investigations of safety and effectiveness (i.e., an NDA), where at least some of the information required for approval comes from studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference or use (i.e., published literature or FDA's prior finding of safety and/or effectiveness for one or more listed drugs). 21 U.S.C. § 355(b)(2). A 505(b)(2) applicant may rely on FDA's finding of safety and effectiveness for a listed drug only to the extent that the product in the 505(b)(2) application shares characteristics with the listed drug(s), such as active ingredient, dosage form, route of administration, strength, indication, or conditions of use. The 505(b)(2) application must include sufficient data to support any differences between the proposed drug and the listed drug(s) and demonstrate that the proposed drug product meets the statutory approval standard for safety and effectiveness.

The timing for approval of both 505(b)(2) applications and ANDAs depends, in part, on statutory patent protections afforded to the previously approved drug product(s) on which the applicant relies. 505(b)(2) and ANDA applicants must submit one of four specified certifications

[5] This previously approved drug is called the reference listed drug ("RLD"), defined as "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application." 21 C.F.R. § 3l4.3(b).

for each patent that claims the listed drug or a method of using the drug for which the applicant is seeking approval, and for which information is required to be filed under section 355(b)(1) or 355(c)(2) of the FDCA. *See* 21 U.S.C. § 355(b)(2)(A)-(B), (j)(2)(A)(vii)-(viii).

If a certification is made under paragraph I or II indicating, respectively, that patent information pertaining to the drug or its use has not been filed with FDA or that the patent has expired, the 505(b)(2) application or ANDA may be approved immediately. 21 U.S.C. § 355(c)(3)(A), (j)(5)(B)(i). A paragraph III certification indicates that the applicant does not intend to market the drug until after the applicable patent has expired, and approval of the 505(b)(2) application or ANDA may be made effective on the patent expiration date. 21 U.S.C. § 355(c)(3)(B), (j)(5)(B)(ii).

If an applicant wishes to challenge the validity of a patent, or to claim that the patent would not be infringed by the product or use covered by the 505(b)(2) application or ANDA, the applicant must submit a certification pursuant to paragraph IV. *See* 21 U.S.C. § 355(b)(2)(A)(iv), (j)(2)(A)(vii)(IV). The applicant must also provide notice of its paragraph IV certification to the NDA holder for the listed drug and each patent owner explaining the factual and legal basis for the applicant's opinion that the patent is invalid or not infringed. 21 U.S.C. § 355(b)(3), (j)(2)(B).

The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of infringement. 35 U.S.C. § 271(e)(2)(A). This enables the NDA holder and patent owner to sue the 505(b)(2) or ANDA applicant. If such a suit is brought within 45 days of the date notice of the certification was received by the patent owner or NDA holder, FDA must stay approval of the 505(b)(2) application or ANDA for 30 months from that date (commonly referred to as the "30-month stay"), unless a final court decision is reached

earlier in the patent case or the court orders a longer or shorter period. 21 U.S.C. § 355(c)(3)(C), (j)(5)(B)(iii). If no action is brought within the 45-day period, FDA may approve a 505(b)(2) application or ANDA with a paragraph IV certification effective immediately, provided that the other conditions for approval have been met. *Id.*

FACTUAL BACKGROUND

I. COLCHICINE

Colchicine is an alkaloid derived from the Colchicum autumnale plant (also known as autumn crocus or meadow saffron) that has been used in small doses for gout prophylaxis since the 1930s.[6] Compl. Ex. 1 at 3-4. In 1961, Merck Sharp & Dohme received approval for NDA 12-383 for ColBenemid, a fixed combination drug product that contains probenecid (500 mg) and colchicine (0.5 mg). *Id.* This approval pre-dated the 1962 amendments to the FDCA, which required that drugs be proven to be effective as well as safe. After the passage of these amendments, FDA initiated the Drug Efficacy Study Implementation ("DESI") review to evaluate the effectiveness of drugs, such as ColBenemid, that had been previously approved on safety grounds alone. *Id.* In its DESI review of ColBenemid, FDA concluded that NDA 12-383 for probenecid with colchicine is "effective for the treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout." 37 Fed. Reg. 15189-02 (July 28, 1972). In 1976, Danbury Pharmacal, Inc. received approval for ANDA 84-279 for Col-Probenecid, a tablet that contained 500 mg of probenecid and 0.5 mg of colchicine, based on FDA's previous approval of ColBenemid and the DESI finding of effectiveness. Compl. Ex. 1 at 4.

The widespread use of colchicine for treatment of acute gout flares and prophylaxis of

[6] Colchicine was originally marketed as an unapproved drug.

gout flares led to the recognition of its potential toxicities, which are described in rheumatology textbooks, published guidelines, and scientific literature. Compl. Ex. 1 at 5. Colchicine toxicity is dose-related. *Id.*

II. COLCRYS

On July 29, 2009, NDA 22-352 for Colcrys (colchicine) 0.6-mg tablets was approved for the treatment of FMF. Compl. Ex. 1 at 6. The approval of this 505(b)(2) application was based on published literature describing the safety and effectiveness of colchicine for this indication and additional safety data consisting of a summary of the adverse event reporting to FDA and the World Health Organization databases. *Id.* This NDA was also supported by two drug-drug interaction studies (i.e., studies on the risk of colchicine toxicity caused by the interaction of colchicine and another drug product when the drugs were taken concurrently) completed by the NDA's sponsor, Mutual. *Id.*

On July 30, 2009, FDA approved a second 505(b)(2) application for Colcrys (NDA 22-351) for the treatment of acute gout flares. Compl. Ex. 1 at 6. The approval was based on Mutual's clinical trial (the AGREE trial) that evaluated the efficacy, safety, and tolerability of colchicine in patients with an acute gout flare, and on published literature describing the results of an earlier clinical study of colchicine in acute gout. *Id.* Although adverse event reports and published literature provided some general information on drug-drug interactions with colchicine, the drug-drug interaction studies conducted by Mutual provided data to inform FDA's dosage recommendations for Colcrys. *Id.* at 7. The AGREE trial was essential to the approval of Colcrys for treatment of acute gout flares and, as a result, FDA granted Colcrys a 3-

year period of exclusivity, which expired on July 30, 2012. *Id.*[7]

A third 505(b)(2) application for Colcrys (NDA 22-353) was approved for prophylaxis of gout flares on October 16, 2009. Compl. Ex. 1 at 8. Seventeen method-of-use patents are listed in connection with NDA 22-352 (under which NDAs 22-351 and 22-353 were consolidated). *See* Orange Book, *available at* http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=022352&Product_No=001&table1=OB_Rx (printout attached to complaint at Ex. 17). The earliest of these patents expires on October 6, 2028. *Id.*

III. FDA'S 2011 CITIZEN PETITION RESPONSE

Mutual filed a citizen petition, dated November 26, 2010, regarding requirements for ANDAs and 505(b)(2) applications for colchicine tablets. Compl. Ex. 1 at 1. FDA responded on May 25, 2011, granting the petition in part and denying it in part. *Id.* at 2. FDA concluded:

> FDA grants Mutual's request to require that a marketing application for a duplicate of Colcrys that is eligible for approval under section [355(j)] must be submitted as an ANDA that cites Colcrys as the RLD and complies with applicable regulatory requirements. FDA also grants Mutual's request that FDA refrain from approving any 505(b)(2) application or ANDA for a single-ingredient colchicine product if the application includes a paragraph iv certification and the applicant failed to submit documentation of receipt of notice of paragraph iv certification by each party identified in 21 C.F.R. 314.52(a) or 314.95(a).
>
> FDA denies Mutual's request that any 505(b)(2) application for a single-ingredient oral colchicine product must necessarily cite Colcrys as its listed drug, irrespective of whether the proposed product shares the same strength, pharmacokinetic (PK) profile, or other characteristics such as dosage form or conditions of use. However, any 505(b)(2) application for a proposed single-ingredient colchicine product must meet the statutory approval standard for safety and effectiveness.
>
> FDA grants in part Mutual's request regarding labeling requirements for

[7] Under 21 U.S.C. § 355(c)(3)(E)(iii), a drug sponsor may obtain a 3-year period of exclusivity for conducing new clinical investigations essential to the approval of an application.

> single-ingredient oral colchicine products. 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. In addition, 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, and thus the approval of such a product must await expiration of Colcrys' 3-year exclusivity for acute gout flares on July 30, 2012.
>
> Finally, FDA denies as not warranted Mutual's requests to expand the scope of the current 3-year exclusivity period ending on July 30, 2012, and to receive an additional 3-year exclusivity period.

Compl. Ex. 1 at 2-3. FDA also concluded that the agency should not have allowed West-Ward to file a 505(b)(2) application for a colchicine tablet, 0.6 mg, with a proposed indication already approved for Colcrys. *Id.* at 11-18. Such a product would be a duplicate of Colcrys and therefore should have been submitted in an ANDA. *Id.*

IV. MITIGARE

NDA 204820 for Mitigare (colchicine) capsules, 0.6 mg, for prophylaxis of gout flares was filed on October 5, 2012, and approved on September 26, 2014. Compl. Ex. 10. The Mitigare application was a 505(b)(2) application that relied on FDA's finding of safety and effectiveness for Col-Probenecid, as well as published literature on the safety and efficacy of colchicine as prophylaxis for gout flares and four drug-drug interaction studies conducted by West-Ward. *See* AR at 108. Because Mitigare is a capsule, not a tablet, it has a different dosage form and thus is not considered a duplicate of Colcrys.

V. COURT ACTION

Takeda initiated a patent infringement action against West-Ward in the Delaware district court on the same day it brought this action against FDA. *See Takeda Pharms. USA, Inc. v. West-Ward Pharm. Corp.*, Civ. No. 14-1268-SLR (D. Del. Oct. 6, 2014). On October 9, the

Delaware court entered a TRO enjoining West-Ward from marketing Mitigare pending further proceedings in the patent litigation. *See id*.

ARGUMENT

Preliminary injunctive relief is an "extraordinary and drastic" remedy that "may only be awarded upon a clear showing that the plaintiff is entitled to such relief." *Winter v. NRDC, Inc.*, 555 U.S. 7, 129 S. Ct. 365, 375-76 (2008); *Munaf v. Geren*, 553 U.S. 674, 128 S. Ct. 2207, 2219 (2008); *see also Mpoy v. Fenty*, 674 F. Supp. 2d 163, 165 (D.D.C. 2009) ("Injunctive relief is an extraordinary remedy, and plaintiff bears a substantial burden to obtain it."). To obtain either a temporary restraining order or a preliminary injunction, a party must establish that: (1) it is likely to succeed on the merits; (2) it is likely to suffer irreparable harm in the absence of preliminary relief; (3) the balance of equities tips in its favor; and (4) an injunction would serve the public interest. *Winter*, 129 S. Ct. at 375; *ABA, Inc. v. D.C.*, 2014 U.S. Dist. LEXIS 64126, *24 (D.D.C. May 9, 2014); *see also Hall v. Johnson*, 599 F. Supp. 2d 1, 3 n.2 (D.D.C. 2009) (the same standard applies to both temporary restraining orders and preliminary injunctions).

It is "particularly important" for a movant to demonstrate likely success on the merits. *Astellas Pharma US, Inc., v. FDA*, 642 F. Supp. 2d 10, 16 (D.D.C. 2009) (absent "substantial indication" of likely success, there would be no justification for court's intrusion into ordinary processes of administration and judicial review). Moreover, a party seeking preliminary injunctive relief must demonstrate an actual "likelihood" of success on the merits, not merely the existence of "questions so serious, substantial, difficult and doubtful, as to make them fair ground for litigation . . . ." *Munaf*, 128 S. Ct. at 2219 (citations omitted). Nor is a mere "possibility" of irreparable harm sufficient to justify such relief:

> Our frequently reiterated standard requires plaintiffs seeking preliminary relief to demonstrate that irreparable injury is *likely* in the absence of an injunction. . . .

> Issuing a preliminary injunction based only on a possibility of irreparable harm is inconsistent with our characterization of injunctive relief as an extraordinary remedy that may only be awarded upon a clear showing that the plaintiff is entitled to such relief.

Winter, 129 S. Ct. at 375-76 (citations omitted, emphasis in original).

In this case, Takeda's burden is even higher, because it seeks not to preserve the *status quo*, but instead to obtain an order requiring immediate suspension of approval of a competitor's product. A court's power to issue such a mandatory injunction "should be sparingly exercised." *Mylan Pharms., Inc. v. Shalala*, 81 F. Supp. 2d 30, 36 (D.D.C. 2000).

I. TAKEDA HAS NO LIKELIHOOD OF SUCCESS ON THE MERITS

A. Arbitrary And Capricious Standard Of Review

FDA's administrative decisions are subject to review under the Administrative Procedure Act, and may be disturbed only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). This standard is highly deferential to the agency. *Citizens to Pres. Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971). The agency's administrative decision is entitled to a presumption of validity. *Fla. Power & Light Co. v. Lorion*, 470 U.S. 729, 743 (1985); *Camp v. Pitts*, 411 U.S. 138, 142 (1973). The reviewing court must consider whether the agency's decision was based upon consideration of the relevant factors and whether there has been a clear error of judgment. *Overton Park*, 401 U.S. at 416. However, a reviewing court is "not empowered to substitute its judgment for that of the agency," *id.*, and must uphold the agency's action so long as it is "rational, based upon consideration of the relevant factors and within the scope of the authority delegated to the agency by the statute." *Motor Vehicle Mfrs. Ass'n, Inc., v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42 (1983).

In addition, when an agency's decision is based on evaluation of scientific information within the agency's area of technical expertise, its decisions are traditionally accorded great

deference. *See Am. Wildlands v. Kempthorne*, 530 F.3d 991, 1000 (D.C. Cir. 2008) ("The rationale for deference is particularly strong when the [agency] is evaluating scientific data within its technical expertise") (quoting *Int'l Fabricare Inst. v. EPA*, 972 F.2d 384, 389 (D.C. Cir. 1992)); *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (courts "review scientific judgments of the agency 'not as the chemist, biologist, or statistician that [they] are qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality.'") (quoting *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976)); *Sw. Pa. Growth Alliance v. Browner*, 121 F.3d 106, 117 (3d Cir. 1997) (reviewing court must generally be "at its most deferential" when reviewing factual determinations within an agency's area of special expertise; it is not the role of a reviewing court to second-guess agency's scientific judgments). Such deference has repeatedly been applied in cases under the FDCA. *See, e.g., Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998) ("FDA's determination of what is required to establish 'sameness' for purposes of the Act rests on the 'agency's evaluations of scientific data within its area of expertise,' and hence is entitled to a 'high level of deference' from this court.") (quoting *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995)); *Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996) ("FDA possesses the requisite know-how to conduct such [scientific] analyses, by sifting through the scientific evidence to determine the most accurate and up-to-date information regarding a particular drug . . . . We therefore defer to its reasonable findings."); *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) (FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us."); *Tri-Bio Labs., Inc. v. United States*, 836 F.2d 135, 142 (3d Cir. 1987) ("We are mindful that in evaluating scientific evidence in the drug field,

the FDA possesses an expertise entitled to respectful consideration by this court."), *cert. denied*, 488 U.S. 818 (1988).

B. Takeda Has Not Shown That FDA Erred In Approving Mitigare

Takeda contends that FDA acted arbitrarily and capriciously by not requiring West-Ward to include dosing modifications found on the Colcrys labeling on the Mitigare labeling. *See*, *e.g.*, Takeda Br. at 1. Takeda claims that the absence of such information from the Mitigare labeling renders the product unsafe and that FDA therefore should not have approved Mitigare. *Id.*

Mitigare's labeling warns of potential drug-drug interactions and contains dosing modifications aimed at reducing the risk of colchicine toxicity (*see* Compl. Ex. 2 at 1, 2) – which is precisely what FDA said in its 2011 citizen petition response would be required for all single-ingredient colchicine products. *See* Compl. Ex. 1 at 3, 19-20. Mitigare's warnings about drug-drug interactions and relevant dose adjustments are different than Colcrys' because each company conducted its own drug-drug interaction studies to support labeling for the indication(s) for which it sought approval, and each product's labeling reflects the results of studies submitted as well as information from published literature. *See* Compl. Exs. 2 (Mitigare label), 5 (Colcrys label). West-Ward's drug-drug interaction studies showed that Mitigare did not significantly interact with the drugs studied, an unexpected result given the opposite results reached in Takeda's drug-drug interaction studies of Colcrys, and the fact that colchicine's drug-drug interaction potential had long been reported in the scientific literature. *See* AR at 96 (attached as Exhibit C), 667 (attached as Exhibit D). After ruling out other possible explanations for West-Ward's (unexpected) results and carefully reviewing West-Ward's drug-drug interaction study data, FDA concluded that the drugs West-Ward used in its studies, which were different than the drugs used by Takeda in its drug-drug interaction studies, were the likely explanation. AR at 96-

97; *see also* AR at 670. FDA thus concluded that specific dose modifications were not warranted when Mitigare was taken concurrently with the drugs used in West-Ward's drug-drug interaction studies, and Mitigare's labeling reflects this scientific conclusion. *See* AR at 670.

Takeda attempts to conflate general language from FDA's citizen petition response, 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," Comp. Ex. 1 at 19-20, into a requirement that any single-ingredient oral colchicine product contain the same dosing modifications as Colcrys. But FDA had not yet reviewed West-Ward's data when it wrote that response. FDA's approval of Mitigare represents the agency's conclusion, based on scientific review of data in West-Ward's NDA, that the dosing modifications and drug-drug interaction warnings in Mitigare's labeling are appropriate, and sufficient to ensure that Mitigare is safe and effective for its intended use. *See* Compl. Ex. 10; *see also* AR at 119-120, 97-98. The Mitigare labeling thus comports with the agency's 2011 citizen petition response because it contains "adequate information on drug-drug interactions" and dosing adjustments relevant to Mitigare. FDA's approval of Mitigare does not "amount[] to an abrupt about-face of its previous position," Takeda Br. at 22, much less an unexplained change in position, as Takeda claims.

Takeda also contends that FDA's 2011 citizen petition response requires that "even a product indicated *only* for prophylaxis [of gout flares] need[s] to include the low-dose treatment for acute gout flares," Takeda Br. at 20 (emphasis added), a method of use that Takeda asserts is protected by patent(s) held by Takeda. In fact, the citizen petition response states: "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

[conducted by Mutual] is adequate to treat an acute gout flare that may occur during chronic colchicine use." Compl. Ex. 1 at 3, 24. At the time FDA wrote this sentence, the agency had not considered the possibility that product labeling for a single-ingredient colchicine product would expressly disclaim use for acute treatment of gout flairs during prophylaxis. Mitigare, however, is not approved for treatment of acute gout flares, including the acute treatment of gout flares that may occur during prophylaxis, and Mitigare's label and accompanying Medication Guide state this unequivocally. *See* Compl. Ex. 2 ("[t]he safety and effectiveness of Mitigare for acute treatment of gout flares during prophylaxis has not been studied"); *see also* AR at 113 ("Although the applicant [West-Ward] is not seeking an indication for the treatment of acute gout flares, to the extent that a healthcare provider may be considering use of additional Mitigare for treatment of an acute gout flare in a patient receiving Mitigare for prophylaxis, the review team determined that it would be appropriate for the label to note that Mitigare should not be used in this way, as it has not been studied.")]. Because 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. Takeda has not, and cannot, show that product labeling must contain instructions for a use for which a product is expressly not approved.

Takeda's sole argument to support its contention that Mitigare is unsafe is that Mitigare's labeling differs from the Colcrys labeling. *See* Takeda Br. at 23. But the Mitigare labeling explains the potential toxicities that can result from the interaction of colchicine and certain other products, *see* Compl. Ex. 2 at 3-4, and describes the four drug-drug interaction studies conducted by West-Ward. *See id.* at 4, 7-8. FDA did not ignore the potential risk of interactions with concomitant use of colchicine and certain other drug products, as Takeda contends. Takeda Br. at 25. Instead, the data and information submitted in West-Ward's application for Mitigare

supported the use of drug interaction information in its labeling that is less specific than that approved for Colcrys'. *See* AR at 119-120. Indeed, FDA's review of the Mitigare application noted that in light of the new data that West-Ward submitted, "it may not be appropriate to recommend precise dose modifications based on currently available drug-drug interaction information for colchicine." AR at 120; *see also* AR at 672 ("the West-Ward [drug-drug interaction] studies raise questions about the generalizability of detailed dose modification recommendations to drugs that have not been directly studied"); AR at 97-98 (West-Ward's drug-drug interaction study results brought to light an "uncertainty regarding whether specific dose modifications may be applicable for a given scenario, and whether they would result in improved safety over simpler recommendations for close monitoring and dose adjustment based on clinical judgment."). FDA thus concluded in light of the scientific evidence submitted by West-Ward that drug interaction and dose modification warnings of a more general nature than those set forth in the Colcrys labelling would be most appropriate for Mitigare. These differences in labelling do not somehow render Mitigare less safe than Colcrys, and Takeda's speculation to the contrary provides no basis for questioning FDA's scientific judgment that Mitigare is fully safe and effective for its approved indication.

Takeda's claim that FDA violated its procedural "right" to participate in an administrative process fares no better. As Takeda itself acknowledges, *see* Takeda Br. at 4, it is entirely appropriate for an applicant to submit a 505(b)(2) application for a product that has a different dosage form than the previously approved drug. Because Mitigare is a capsule and Colcrys is a tablet, Mitigare is not a duplicate of Colcrys; West-Ward was permitted to seek approval with a 505(b)(2) application rather than an ANDA. Like the Colcrys application, the listed drug on which the Mitigare application relied was a previously-approved colchicine

product.[8] Indeed, FDA expressly stated in its 2011 citizen petition response that the agency would not require all future applications seeking approval of a colchicine product to reference Colcrys:

> [I]n light of the significant amount of non-product-specific published scientific literature on colchicine and additional non-product-specific scientific literature that may become available over time, FDA declines to speculate on whether a 505(b)(2) applicant for a non-pharmaceutically equivalent product could submit adequate safety and effectiveness data to support approval without reference to Colcrys.

Compl. Ex. 1 at 21. Takeda asserts that "Colcrys is the only approved drug product that includes data and labeling sufficient to meet the [relevant] safety standard," Takeda Br. at 28, but this is a baseless assertion. FDA concluded that the 505(b)(2) application for Mitigare met the statutory standard of demonstrating safety and effectiveness for its intended use, *see* Compl. Ex. 10, without relying on Colcrys as the listed drug. *See* AR at 116, 122.

FDA does not dispute that if West-Ward had referenced Colcrys as the listed drug, it would have been required to file certifications to each of the patents listed in the Orange Book for Colcrys. *See* Takeda Br. at 26-29. And if those certifications had been paragraph IV certifications, West-Ward would have been required to notify Takeda, which could have led to a patent infringement suit by Takeda, thereby resulting in a stay of West-Ward's approval for 30 months. Notification of the existence of West-Ward's application could also have prompted Takeda to file a citizen petition with FDA. However, this hypothetical situation did not, in fact, occur. West-Ward is not a duplicate of Colcrys and was not required to reference Colcrys or to

[8] Takeda claims that because both of the colchicine combination products currently listed in the Orange Book were approved as ANDAs, neither "would be considered appropriate for reference in a 505(b)(2) application." Takeda Br. at 28 n.7. Takeda's own NDA for Colcrys for prophylaxis of gout flares, however, relied on FDA's prior finding of safety and effectiveness for Col-Probenecid, the product approved under ANDA 84279 and the very product on which it says it was improper for West-Ward to rely. *See* Compl. Ex. 6 at 2 (FDA's clinical pharmacology and biopharmaceutics review of a Colcrys 505(b)(2) NDA).

certify to its patents. Takeda's purported "right" to participate in the administrative process boils down to a desire to have known about the Mitigare application prior to approval, but Takeda has not cited any authority for the notion that a company is entitled to advance notice of potential competitors' drug approval(s).

In sum, Takeda is unhappy that the approval of Mitigare was not blocked by the patents listed for Colcrys. Without knowledge of the science supporting the West-Ward application, Takeda nonetheless claims that Mitigare cannot possibly be safe with different labeling than Colcrys. After thorough review of the Mitigare application, FDA concluded that Mitigare is safe, and effective, as labeled, and did not act in an arbitrary, capricious, or otherwise unlawful manner when approving Mitigare. All of Takeda's claims thus lack merit.

II. TAKEDA HAS NOT SHOWN THAT IT WILL SUFFER IRREPARABLE INJURY IN THE ABSENCE OF PRELIMINARY RELIEF

Takeda asserts that it will suffer irreparable harm to its goodwill and reputation, as well as irreparable economic harm in the absence of preliminary injunctive relief. Takeda, however, cannot clear the hurdle that only *irreparable* harm that is *likely* to occur justifies the issuance of a preliminary injunction, *Winter*, 129 S. Ct. at 376. "Indeed, if a party fails to make a sufficient showing of irreparable injury, the court may deny the motion for injunctive relief without considering the other factors." *Astellas*, 642 F. Supp. 2d at 16. As Judge Kavanaugh has pointed out, "the *Winter* Court rejected the idea that a strong likelihood of success could make up for showing only a possibility (rather than a likelihood) of irreparable harm. In other words, the Court ruled that the movant always must show a likelihood of irreparable harm." *Davis v. Pension Benefit Guar. Corp.*, 571 F.3d 1288, 1296 (D.C. Cir. 2009) (Kavanaugh, J., joined by Henderson, J., concurring). Irreparable injury is a "very high standard." *Ark. Dairy Coop., Inc. v. USDA*, 576 F. Supp. 2d 147, 160 (D.D.C. 2008); *Bristol*, 923 F. Supp. at 220. The injury

alleged must be certain, great, actual, and imminent, *Wis. Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985), and it must be "more than simply irretrievable; it must also be serious in terms of its effect on the plaintiff." *Gulf Oil Corp. v. Dep't of Energy*, 514 F. Supp. 1019, 1026 (D.D.C. 1981).

Takeda's claims of harm to its reputation are based on the theory that injuries from West-Ward's product will be attributed to Takeda. This feared harm, however, is purely conjectural; irreparable harm must be "'actual and not theoretical.'" *Am. Meat Inst. v. USDA*, 968 F.Supp.2d 38, 75 (D.D.C. 2013) (quoting *Wis. Gas Co.*, 758 F.2d at 674). *ViroPharma, Inc. v. Hamburg*, 898 F.Supp.2d 1, 27 (no reputational injury found where ViroPharma claimed the generic may be "unsafe or ineffective."); *Astellas*, 642 F.Supp.2d at 23 (no irreparable harm where "plaintiff's concerns about the potential loss of goodwill and reputation are founded entirely on its belief that the approved [generic] may be more harmful than [its own product], a belief that lacks evidentiary support and is entirely speculative"); *Bristol*, 923 F.Supp. at 221 (no irreparable harm because "there is nothing before the court which would lead it to conclude that [the competing drug] will cause any harmful health effects"). Takeda's speculative allegations are insufficient to demonstrate irreparable harm.

Takeda's claims related to a loss of goodwill as a result of "the perception that Takeda is causing a generic product to be taken off the market" similarly fail to establish irreparable harm. Much like Takeda's claims of potential injury to its reputation, these claims are speculative, and based only upon what happened when other colchicine products were taken off the market years ago. Additionally, the harm Takeda is alleging here, if real, has already occurred by virtue of the filing of this lawsuit, which publically seeks to remove a competing, lower-cost product from the market. As a result, Takeda's speculation about public perception cannot satisfy the requirement

that the harm be "imminent." *Wis. Gas Co.*758 F.2d at 674 ("The movant must provide proof that the harm has occurred in the past and is likely to occur again, or proof indicating that the harm is certain to occur in the near future."); *see also O.K. v. Bush* 377 F. Supp.2d 102, 114, (D.D.C. 2005) (plaintiff demonstrated past harm and mistreatment, but no reason to believe that it will reoccur "again in the near future.") "Further, the movant must show that the alleged harm will directly result from the action which the movant seeks to enjoin." *Wis. Gas Co.*758 F.2d at 674. Although it is dubious whether the "perception" Takeda fears would *irreparably* damage the reputation and goodwill of a global corporation with multiple product lines in dozens of countries around the world, granting a PI would not prevent such alleged harm from occurring in any event – that bell has already been rung with the filing of this lawsuit.

Finally, Plaintiff's claims related to economic harm do not satisfy the "very high bar" that must be met to establish irreparable harm. *Am. Meat Inst.*, 968 F.Supp.2d at 75. In this circuit, mere economic loss—even irrecoverable economic loss, such as Takeda alleges here—does not constitute irreparable harm unless the financial injury is so great as to threaten the continued existence of the movant's business:

> To satisfy the standard of irreparable injury to justify a preliminary injunction, the movants' loss must be "more than simply irretrievable." *Mylan Labs., Inc. v. Thompson*, 139 F. Supp. 2d 1, 27 (D.D.C. 2001); *see also Wisc. Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985). Instead, the injury must be such that it "cause[s] extreme hardship to the business, or even threaten[s] destruction of the business." *Gulf Oil Corp. v. Dep't of Energy*, 514 F. Supp. 1019, 1025 (D.D.C. 1981); *see also, Sandoz, Inc. v. FDA*, 439 F. Supp. 2d 26 (D.D.C. 2006) (noting that "[t]o successfully shoehorn potential economic loss into the irreparable harm requirement, a plaintiff must establish that the economic harm is so severe as to 'cause extreme hardship to the business' or threaten its very existence.").

Mylan Labs., Inc. v. Leavitt, 484 F. Supp. 2d 109, 123 (D.D.C. 2007); *see also Am. Meat Inst.*, 968 F. Supp. 2d at 76-77 ("[t]o successfully shoehorn potential economic loss into a showing of irreparable harm, a plaintiff must establish that the economic harm is so severe as to cause

extreme hardship to the business or threaten its very existence."); *Astellas*, 642 F. Supp. 2d at 22 ("it is well-settled that economic loss alone will rarely constitute irreparable harm"); *Hi-Tech Pharmacal Co. v. FDA*, 587 F. Supp. 2d 1, 11 (D.D.C. 2008) ("In this jurisdiction, harm that is 'merely economic' in character is not sufficiently grave under this standard."); *Coal. for Common Sense in Gov't Procurement v. United States*, 576 F. Supp. 2d 162, 168-69 (D.D.C. 2008) (finding that "degree of harm" asserted by coalition of pharmaceutical manufacturers did not approach "the level required in this case (*i.e.* so severe as to cause extreme hardship to the business or threaten the very existence of Coalition members)"); *Apotex, Inc. v. FDA*, No. 06-0627 (JDB), 2006 WL 1030151 (D.D.C. Apr. 19, 2006) at * 17 (where plaintiff did not establish that lost sales and market share would cause "extreme hardship" to company, claim of harm fell "well short of the serious, irretrievable damage to its business required to warrant a preliminary injunction"); *Sociedad Anonima Vina Santa Rita v. Dep't of Treasury*, 193 F. Supp. 2d 6, 14 (D.D.C. 2001) ("financial harm alone cannot constitute irreparable injury unless it threatens the very existence of the movant's business").

Thus, in order to prevail on a motion for emergency relief, Takeda must make "a strong showing" that any economic loss it would suffer in the absence of such relief "would significantly damage its business above and beyond a simple diminution in profits." *Mylan v. Shalala*, 81 F. Supp. 2d at 42-43; *see also Wash. Metro. Area Transit Comm'n v. Holiday Tours, Inc.*, 559 F.2d 841, 843 n. 3 (D.C. Cir. 1977) ("The mere existence of competition is not irreparable harm, in the absence of substantiation of severe economic impact.").

Takeda does not come close to satisfying this standard. Takeda's claimed irreparable harm is that the approval of Mitigare causes it to "lose the value of its investment" in developing, patenting, and promoting its colchicine product. Takeda also attempts to quantify the actual loss

it may suffer due to generic competition as a result of West-Ward's product entering the market.[9] While Takeda redacted net sales figures from its public TRO filings, Takeda's website reports sales figures for Colcrys. (*Available at* http://www.takeda.com/investor-information/highlights/products.html). Specifically, it lists FY13 sales totaling 51.9 billions of yen, and estimated FY14 sales of 60.0 billions of yen. These sums convert to FY13 sales of approximately $478 million dollars and estimated FY14 sales of approximately $553 million.

In its filing, Takeda compares these sums to Takeda's "profit before taxes" in sales made only in the United States. This is not an appropriate comparison. The plaintiff here, Takeda Pharmaceuticals USA, is part of a large, global corporation, and its financials must be viewed as such.[10] *See Mylan v. Leavitt*, 484 F. Supp.2d at 123 ("[m]onetary figures are relative, and depend for their ultimate quantum, on a comparison with the overall financial wherewithal of the corporation involved."). Takeda's worldwide revenue for FY13 was 1,691.7 billion yen and its estimated FY14 revenue is 1,725.0 billion yen. (*Available at* http://www.takeda.com/investor-information/highlights/). When converted to U.S. dollars, Takeda's FY13 revenue was approximately $15.6 billion and it is currently estimating $15.9 billion in revenue for FY14. In sum:

	Revenue from Colcrys	**Total Revenue**	**% of Total Revenue**
FY13	$478 million	$15.6 billion	3%
FY14 (est.)	$553 million	$15.9 billion	3%

This chart demonstrates that the revenues Takeda receives from the sale of its colchicine product do not constitute a substantial portion of its total revenue. The loss of revenue from this

[9] Presumably Takeda's claimed loss has decreased now that the Delaware court has entered a TRO against West-Ward in the patent infringement case.

[10] According to its website, Takeda Pharmaceuticals USA is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited and was founded in 1998 to accelerate Takeda's global expansion into the U.S. market. Even in its own right, Takeda USA ranks among the top 15 pharmaceutical companies in the United States. *See* http://www.takeda.us/.

single product over the short period of time it will take this case to be resolved on the merits would not constitute a loss that "would threaten the continued existence of [Takeda's] business." *Mylan*, 484 F. Supp. 2d at 123.

Takeda also argues that the economic harm it faces is irreparable because it will not be able to recoup its economic losses from FDA if this suit is resolved in its favor.[11] However, while some courts have held that economic losses can constitute irreparable injury where they are unrecoverable, the "'fact that economic losses may be unrecoverable does not, in and of itself, compel a finding of irreparable harm,' for the harm must also be 'more than simply irretrievable; it must also be serious in terms of its effect on the plaintiff.'" *Safari Club International v. Jewell*, No. 14-0670, 2014 WL 2535948 (D.D.C. June 6, 2014) (*quoting Nat'l Mining Ass'n v. Jackson*, 768 F. Supp. 2d 34, 53 (D.D.C. 2011); *Mylan*, 81 F.Supp.2d at 42); *see also ViroPharma*, 898 F. Supp. 2d at 26 ("irreparability aside, it remains incumbent on plaintiffs to demonstrate, first, that they are threatened with serious injury."). Takeda cannot meet this standard for the economic harm it alleges. Takeda's sales of Colcrys constitute only 3% of its total annual revenue, and the loss of some small portion of this revenue for the short time it will take to resolve this matter on the merits will not constitute a serious injury to Takeda. For all of these reasons, Takeda cannot meet its burden of establishing that it will suffer irreparable injury in the absence of preliminary injunctive relief.

III. THE BALANCE OF HARMS AND THE PUBLIC INTEREST WEIGH AGAINST THE ENTRY OF PRELIMINARY RELIEF

Takeda has also failed to show that any harm it may suffer in the absence of injunctive relief outweighs the potential harm to FDA and the public. Although FDA has no commercial

[11] Takeda neglects to inform the Court that it is seeking monetary relief from West-Ward in the Delaware lawsuit for any economic losses it may suffer.

stake in the outcome of this litigation, FDA's interest and the public's interest in drug approvals are the same. *See Serono*, 158 F.3d at 1326 (determining that the public interest is "inextricably linked" to Congress's purpose in passing the Hatch-Waxman Amendments). FDA must implement the statutory scheme governing the approval of drugs in the manner outlined by Congress in the FDCA.

In addition, any financial harm that Takeda would incur in the absence of a preliminary injunction will be matched, if not exceeded, by the financial harm that West-Ward will suffer by being deprived of its right to market its product during the period that a PI is in effect. The D.C. Circuit has found in similar circumstances that the balance of harms "results roughly in a draw." *Serono*, 158 F.3d at 1326; *see also Bristol-Myers*, 923 F. Supp. at 221 (noting that generic company had "endured a seven year process to obtain FDA approval" and that "the effect of an injunction [on the generic company] . . . would be dramatically greater" than the harm to plaintiff); *cf. Ark. Dairy Coop.*, 576 F. Supp. 2d at 161 (noting that any harm plaintiffs would suffer absent preliminary injunctive relief would be offset by substantial harm to defendant-intervenors if injunction were granted).

CONCLUSION

For the foregoing reasons, Takeda's motion for a temporary restraining order and/or preliminary injunction should be denied.

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CERTIFICATE OF SERVICE

I certify that on October 17, 2014, I caused a true and correct copy of the above-entitled DEFENDANTS' OPPOSITION TO PLAINTIFF'S MOTION FOR A TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION to be served via the Court's Electronic Case Filing system to counsel for the plaintiff and intervenor as follows:

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