UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

TAKEDA PHARMACEUTICALS, U.S.A., INC., Plaintiff, v. SYLVIA MATHEWS BURWELL, in her official capacity as SECRETARY, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, *et al.*, Defendants, and HIKMA PHARMACEUTICALS PLC, *et al.*, Intervenor-Defendants.	)	Civil Action No. 14-cv-1668 (KBJ) **UNDER SEAL**

AND

ELLIOTT ASSOCIATES, L.P., *et al.*, Plaintiffs, v. SYLVIA MATHEWS BURWELL, in her official capacity as SECRETARY, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, *et al.*, Defendants, and HIKMA PHARMACEUTICALS PLC, *et al.*, Intervenor-Defendants.	)	Civil Action No. 14-cv-1850 (KBJ) **UNDER SEAL**

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MEMORANDUM OPINION

The Hatch-Waxman Amendments to the Food, Drug, and Cosmetic Act ("FDCA"), Pub. L. No. 98-417, 98 Stat. 1585 (1984), "balance two competing interests in the pharmaceutical industry: (1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market." *Janssen Pharmaceutica, N.V. v. Apotex, Inc.*, 540 F.3d 1353, 1355 (Fed. Cir. 2008) (internal quotation marks and citation omitted). Hatch-Waxman achieves this balance, in part, by allowing new applicants for drug approval to rely on research and data that an innovator company generates so long as the new applicant "references" the innovator's drug and "certifies" to the innovator's patents. *See infra* Part I.B.2; *see also* 21 U.S.C. § 355(b)(2)(A). Plaintiffs Takeda Pharmaceuticals U.S.A., Inc. ("Takeda") and Elliott Associates, L.P., Elliott International, L.P., and Knollwood Investments, L.P. (collectively, "Elliott") allege that the Food and Drug Administration ("FDA") upset Hatch-Waxman's careful balance when the agency approved an application that Hikma Pharmaceuticals PLC ("Hikma") submitted through its U.S. agent West-Ward Pharmaceuticals Corp. ("West-Ward") for a gout medication named Mitigare. Mitigare is a single-ingredient 0.6 milligram ("mg") oral colchicine drug product that is substantially similar to Plaintiffs' colchicine drug, Colcrys, which FDA approved five years prior to Mitigare based in part on research studies that Takeda's predecessor Mutual Pharmaceutical Company, Inc. ("Mutual") conducted. In seeking approval for Mitigare, West-Ward neither referenced Colcrys nor certified to the Colcrys patents, and Hikma has now authorized West-Ward to market a generic version of Mitigare that will compete with—and cost less than—Plaintiffs' Colcrys.

In the separate but consolidated complaints that Takeda and Elliott have filed in this Court against Defendants Sylvia Mathews Burwell (in her official capacity as Secretary of the Department of Health and Human Services) and Margaret Hamburg (in her official capacity as head of the FDA), Plaintiffs maintain that FDA's approval of Mitigare without a Colcrys reference or the related patent certifications violates the Administrative Procedure Act ("APA") because that approval was inconsistent with the agency's procedural rules and the certification provisions of the FDCA. Plaintiffs also claim that FDA's approval of Mitigare was arbitrary and capricious because Mitigare's label lacks certain safety information that is on the Colcrys label—information that is related to Mutual's research and that FDA previously suggested should be on the label of future colchicine drug products. The lawsuits that Takeda and Elliott have filed (and in which Hikma and West-Ward have now intervened) request a stay or rescission of FDA's approval of Mitigare as a remedy for these alleged violations.

Before this Court at present are four cross-motions for summary judgment that the Plaintiffs, the Defendants, and the Defendant-Intervenors have submitted in the context of the two pending actions.[1] This Court has considered these dispositive motions, the oppositions thereto, the supplemental briefing, and the arguments made orally at the two hearings that this Court has held in relation to this matter. Because this Court agrees with Defendants and Defendant-Intervenors that (1) no statute,

[1] Takeda originally filed a motion for a preliminary injunction against Burwell and Hamburg on October 6, 2014. (*See* Mot. for TRO or Prelim. Inj., Takeda Pharms. U.S.A., Inc. v. Burwell, et al., No. 14-1668-KBJ (D.D.C. Oct. 6, 2014), ECF No. 9.) That same day, Takeda also initiated a patent infringement action against Hikma and West-Ward in the United States District Court for the District of Delaware. (*See* Compl., Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp. et al., No. 14-1268-SLR (D. Del. Oct. 6, 2014.) In light of subsequent developments in the parallel patent litigation that prohibited Hikma and West-Ward from marketing Mitigare, this Court consolidated Takeda's motion for a preliminary injunction with the resolution of the merits of Takeda's complaint and converted Takeda's motion for a preliminary injunction into a motion for summary judgment. (*See* Order, Takeda Pharms. U.S.A., Inc. v. Burwell, et al., No. 14-1668-KBJ (D.D.C. Nov. 5, 2014), ECF No. 40.)

regulation, or policy required FDA to reject West-Ward's application for Mitigare because the application did not reference Colcrys or certify to the Colcrys patents; (2) FDA's scientific judgment that Mitigare is safe as labeled is well-reasoned and entitled to deference; and (3) FDA did not make an unreasoned change in policy when it approved Mitigare, Takeda's Motion for Summary Judgment in Takeda Pharmaceuticals U.S.A., Inc. v. Burwell, No. 14-1668-KBJ (D.D.C.), is **DENIED**; Elliott's Motion for Summary Judgment in Elliott Associates, L.P. v. Burwell, No. 14-1850-KBJ (D.D.C.), is **DENIED**; and Defendants' and Defendant-Intervenors' cross-motions for summary judgment in Elliott Associates, L.P. v. Burwell, No. 14-1850-KBJ (D.D.C.), are **GRANTED**. This Court issued a separate order consistent with this opinion on January 9, 2015.

I. BACKGROUND

The instant dispute involves two drug products, both of which have the active ingredient colchicine, which is a pharmacological substance that has been used historically for the treatment of gout.[2] Plaintiffs have a financial interest in Colcrys—an FDA-approved 0.6 mg single-ingredient oral colchicine tablet—and they have brought this challenge to Defendant FDA's recent approval of Intervenors' Mitigare, which is a 0.6 mg single-ingredient oral colchicine capsule. In order to understand the Plaintiffs' challenge fully, some background information about both colchicine itself and FDA's prior approval of Plaintiff's Colcrys, is necessary. The underlying facts are not in dispute.

[2] "Gout is a common metabolic disorder characterized by chronically elevated uric acid levels (hyperuricemia) . . . . These deposits of uric acid crystals characteristically trigger intense but self-limited bouts of acute arthritis and over time also may lead to a chronic inflammatory and erosive arthritis and, in some patients, kidney stones." (Admin. R. (hereinafter, "AR") at 4.)

A. Colchicine: A Drug For The Treatment Of Gout

Doctors have used colchicine—an agent derived from the *Colchicum Autumnale* plant—to treat gout for centuries. (*See* Admin. R. (hereinafter, "AR") at 3 ("The first use of colchicine as a selective treatment for gout is attributed to the Byzantine physician Alexander of Tralles in 6 A.D.").) Colchicine can be used both for the targeted treatment of gout flares ("acute treatment") and for longer-term maintenance treatment that is aimed at preventing flares ("prophylaxis"). (*See id*. at 4, 116-17, 157, 204.) However, there is a relatively small window of doses in which colchicine provides therapeutic benefits without causing severe complications. (*See* AR at 202.) This "narrow therapeutic index" means that minor dosing changes can have a grave effect on patient outcomes because toxic levels of colchicine can be reached relatively quickly and "can result in serious life-threatening adverse events and death." (*Id*.; *see also id*. at 117 (noting that, although colchicine is therapeutic "at doses of approximately 0.015 mg/kg," the drug is "toxic in doses greater than 0.1 mg/kg, and typically lethal at doses of approximately 0.8 mg/kg").) Even doses of colchicine that are within the normal therapeutic range can be toxic if colchicine is used concomitantly with certain other drugs called "CYP3A4 and P-gp inhibitors." (*Id*. at 202.)

Consistent with colchicine's long history, drug manufacturers in the United States marketed a variety of forms and dosages of colchicine for decades prior to Congress's 1962 enactment of amendments to the FDCA that required FDA to "approve" a drug—*i.e.*, to make findings that a drug is safe, effective, and properly labeled—prior to marketing. (*See* AR at 50, 255); *see also* Peter Barton Hutt, et al.,

Food and Drug Law 577 (3rd ed. 2007).[3] After Congress passed the 1962 amendments that established a premarket approval requirement, FDA reviewed a number of drugs that were already on the market, including ColBenemid, which is a combination tablet that contains both 0.5 mg of colchicine and 500 mg of probenecid. (*See* AR at 4, 668.) FDA determined that ColBenemid was "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) (*see also* AR at 50), and approved that product for, "essentially, prophylactic treatment of gout flares" (AR at 668). It subsequently approved a generic version of ColBenemid—known as Col-Probenecid—that is also a tablet with 0.5 mg of colchicine and 500 mg of probenecid and is still on the market today. (*See id*. 4, 349, 353.) Other drug manufacturers have relied upon FDA's findings that colchicine and probenecid effectively treat gout in the context of the agency's approval of ColBenemid and Col-Probenecid, including the two drug companies that have sponsored the colchicine drug products at issue in the instant case. (*See id*. at 4, 8).

Just as combination colchicine products were legally marketed and sold for many years in the pre-approval era, "[s]ingle-ingredient colchicine tablets"—tablets that contain only colchicine and are not combined with another drug—"were available for decades as marketed but unapproved products, in 0.6 mg strength." (*Id*. at 668.) The practice of marketing single-ingredient colchicine products as an unapproved drug continued even after Congress required premarket approval of drugs (*see id*. at 421),

[3] Early versions of the FDCA did not require a drug sponsor to seek premarket approval from the federal government. *See, e.g.*, Pure Food and Drugs Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906); Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified at 21 U.S.C. § 301 et seq.).

and it persisted until at least 2006, when "FDA announced a new drug safety initiative to remove unapproved marketed drugs from the market" (*id*. at 349). FDA undertook this initiative with the knowledge that "[f]or historical reasons, some drugs are available in the United States that lack required FDA approval for marketing[,]" FDA Ctr. For Drug Evaluation & Research, Guidance for FDA Staff and Indus.: Marketed Unapproved Drugs—Compliance Policy Guide Sec. 440.100: Marketed New Drugs Without Approved NDAs & ANDAs 2 (June 2006, as revised Sept. 2011), and with the intent to bring all prescription drug products into compliance with an FDA approval process that Congress had adopted in 1984, as part of a statute that is formally named the "Drug Price Competition and Patent Term Restoration Act of 1984" and is commonly referred to as the "Hatch-Waxman Amendments." Pub. L. No. 98-417, 98 Stat. 1585 (1984), codified at 21 U.S.C. § 355.

B. FDA's Drug Approval Framework: The Hatch-Waxman Amendments

In brief, Hatch-Waxman requires drug manufacturers seeking to market a new drug to first obtain FDA approval via one of three different application pathways: (1) a full New Drug Application ("NDA"); (2) an Abbreviated New Drug Application ("ANDA"); or (3) an intermediate process known as a Section 505(b)(2) NDA. *See* 21 U.S.C. § 355; *see also, e.g.*, *Ethypharm S.A. France v. Abbott Labs*, 707 F.3d 223, 226-27 (3d Cir. 2013) (describing the three different approval methods).

1. NDAs, ANDAs, and 505(b)(2) NDAs

The full NDA process, *see* 21 U.S.C. § 355(b)(1), requires the manufacturer to submit detailed safety and efficacy data for the drug, including, among other things, "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use" (*i.e.*, clinical trials); all

components of the drug; the methods used for the drug's manufacture, processing, and packing; examples for proposed labeling for the drug; and any patents claimed in relation to the drug. *See* 21 U.S.C. §§ 355(b)(1)(A), (B), (D), (F), (G). This path is used by drug manufacturers for "new branded drug[s]," *Ethypharm S.A. France*, 707 F.3d at 226, which are sometimes called "pioneer" or "innovator" drugs.

A drug manufacturer may also choose to file an Abbreviated New Drug Application ("ANDA") pursuant to 21 U.S.C. § 355(j). The ANDA process facilitates efficient approval of generic versions of pioneer drug products that have already been determined to be safe and effective. Rather than requiring generic manufacturers to conduct expensive and time consuming clinical trials, the ANDA process allows the manufacturer to rely on the clinical trials already performed in connection with the approval of the previously approved drug, provided that the generic manufacturer can show that its drug has the same relevant characteristics (including, *inter alia*, the same labeling, active ingredient, route of administration, dosage form, strength, and bioequivalency). *See* 21 U.S.C. § 355(j)(2)(A). In other words, an ANDA does not attempt to demonstrate safety or effectiveness; instead, the applicant's only goal is to establish that the generic product is equivalent to another drug that is already known to be safe and effective. Thus, this path is used by drug manufacturers "for the introduction of generic versions of previously approved branded drugs." *Ethypharm S.A. France*, 707 F.3d at 227.

The Section 505(b)(2) NDA is a sort of hybrid of the other two pathways.[4] Like the full NDA, a 505(b)(2) NDA must directly demonstrate that the proposed drug

[4] The 505(b)(2) NDA is sometimes also called a "paper NDA." *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1045 (Fed. Cir. 2010).

product is safe and effective; however, like the ANDA, a 505(b)(2) applicant can rely on clinical studies that were previously submitted to FDA in support of another drug and that were not conducted or licensed by the 505(b)(2) applicant. *See* 21 U.S.C. § 355(b)(2). The drug for which the borrowed studies were conducted is referred to as the "Reference Listed Drug" (RLD), and the RLD-related clinical studies that a Section 505(b)(2) applicant relies upon may be proffered to satisfy the applicant's entire burden of proving safety and effectiveness, or they may only support some of the necessary findings; in the latter case, the applicant can supplement with studies of its own. This means that a Section 505(b)(2) NDA may include the applicant's own research supporting the basic safety and efficacy of the drug in addition to the research studies related to the RLD, or it may rely entirely on the RLD, but, in any event, the Section 505(b)(2) applicant must present information that bears upon the safety and effectiveness of its drug product in light of the difference between the pioneer drug product and the applicant's modification of that drug product. The 505(b)(2) NDA pathway is often used when the new drug differs only slightly from the pioneer drug, and this pathway is often favored by drug manufactures seeking to market drugs that are neither "entirely new" nor "simply a generic version of a branded drug." *Ethypharm S.A. France,* 707 F.3d at 227.

2. The Patent Certification Requirement

Because development of a new drug product is notoriously "expensive and time-consuming[,]" *Pfizer Inc. v. Shalala*, 182 F.3d 975, 976 (D.C. Cir. 1999), Congress has concluded that the statutory scheme should include effective incentives for innovation such as patent protection for the substantial "investments necessary to research and develop new drug products" that pioneering companies undertake, *Mylan Pharm., Inc.*

v. FDA, 454 F.3d 270, 272 (4th Cir. 2006) (internal quotation marks omitted). With property rights comes the potential for price manipulation, however; and Congress is also perpetually concerned about drug manufacturer monopolies and the rising prices of prescription drugs. The Hatch-Waxman Amendments to the FDCA are aimed at "strik[ing] a balance between [creating] incentives . . . for innovation," on the one hand, and "quickly getting lower-cost generic drugs to market[,]" on the other. *Teva Pharm. Indus. Ltd. v. Crawford*, 410 F.3d 51, 54 (D.C. Cir. 2005). This balance is reflected in statutory process for the FDA's approval of new drugs.

Specifically, the Hatch-Waxman Amendments mandate that the FDA must record patent information about approved drug products in a publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations," which is generally called the "Orange Book," after the color of its cover.[5] If a drug product is the first-approved innovator of its kind, FDA will designate the product as an RLD that other products may later rely upon. Additionally, any 505(b)(2) NDA that is submitted to FDA for approval must identify the previously approved drug that the applicant is relying upon for approval, *see* 21 C.F.R. § 314.54, and must contain certain statements ("certifications") regarding any "product patents" (patents covering a drug product or the drug substance that is a component of the drug product) and "method-of-use patents" (patents covering approved methods of using a drug product) that are listed in the Orange Book for the referenced drug, *see* 21 U.S.C. § 355(b)(2)(A).

Notably, patent certifications are essentially promises that relate to the status of the drug product's patents, as known or understood by the applicant: (I) no such

[5] *See generally* FDA Electronic Orange Book, http://www.accessdata.fda.gov/scripts/cder/ob/ (last visited January 8, 2015).

patents exist, (II) any such patents have expired, (III) the proposed drug will not be marketed before the patents expire, or (IV) any such patents are invalid or will not be infringed by the proposed drug. *See id*. § 355(b)(2)(A)(i)-(iv). This last requirement—often referred to as a "Paragraph IV certification"—is particularly relevant here because Mutual and its affiliates received numerous patents directed to colchicine. Seventeen of these patents are listed in FDA's Orange Book for Colcrys, and the earliest of the Colcrys patents expires on October 6, 2028.[6]

In addition to the obligation to reference the drug upon which the 505(b)(2) application relies and certify to its patents, a 505(b)(2) applicant must also provide notice of any Paragraph IV certification to owner of the RLD and each patent owner, explaining the factual and legal basis for the applicant's opinion that the patent is invalid or not infringed. *See* 21 U.S.C. § 355(b)(3)(C)-(D). This notice enables the owners of the RLD and its related patents to litigate the patent issue *before* FDA approves the 505(b)(2) NDA applicant's new drug product.[7] To this end, upon the filing of a Paragraph IV certification, FDA is required to stay any approval for at least 45 days, and up to 30 months, in order to permit any potential patent litigation to proceed. *See* 21 U.S.C. § 355(c)(3)(C), (j)(5)(B)(iii).

Thus, Congress has permitted new drug applicants to piggyback on the approved research of prior drug manufacturers—and thus forgo costly and time-consuming studies aimed at proving the safety and effectiveness of drug substances that have

[6] *See* Ex. E to Decl. of Matthew D. McGill, Elliott Associates, L.P. v. Burwell, No. 14-1850-KBJ (D.D.C. Nov. 17, 2014), ECF No. 14-2 at 55-57.

[7] The timing of this notice is important. Generic manufacturers can flood the market within hours of obtaining final FDA approval, *see e.g.*, *In re Buspirone Patent Litig.*, 185 F. Supp. 2d 340, 346 (S.D.N.Y. 2002), lessening the effect of any successful patent infringement claim pursued after the FDA approves a new drug.

already been approved—in exchange for requiring those applicants to notify the owners of the drug that the new applicant relies upon so that the drug owner has an opportunity to take steps to protect its patent rights. *See Abbott Labs. v. Young*, 920 F.2d 984, 985 (D.C. Cir. 1990) ("Facing the classic question of the appropriate trade-off between greater incentives for the invention of new products and greater affordability of those products, Congress struck a balance [in the Hatch-Waxman Amendments] between expediting generic drug applications and protecting the interests of the original drug manufacturers.").

3. The Labeling Requirements

In addition to selecting an approval path, as part of the Hatch-Waxman drug approval process drug sponsors must submit to FDA for approval the "proposed text of labeling," 21 C.F.R. § 314.50(c)(2)(i); *see also* 21 U.S.C. § 355(b), including "adequate directions for use," 21 U.S.C. § 352(f)(1). The labeling must contain all material facts and adequate warnings, and the product must be safe for the uses indicated in the labeling. *Id*. §§ 321(n), 352(f), and 352(p). FDA evaluates the information included in the text of the proposed labeling and has the authority to deny a drug application if it finds that the labeling information is not adequate or is false or misleading. *See* 21 U.S.C. § 355(d); 21 C.F.R. §§ 314.125(b)(6) and (b)(8).

C. FDA's Approval Of Colcrys (A Colchicine Tablet)

When FDA finally undertook vigorous enforcement of Hatch-Waxman's drug approval protocol in 2006, colchicine drug products that had previously been marketed as prescription drugs but had not gone through the new approval process were among the many types of pharmaceuticals that were forced to exit the market. (*See* AR at 5, 349.) The two drug companies that are at odds in the instant dispute—Takeda

(previously Mutual) and Hikma (in conjunction with its U.S. agent West-Ward)—had both previously marketed colchicine products as prescription drugs in the U.S., and both companies sought to have those products approved for re-entry into the marketplace.[8]

On July 31, 2006, Mutual met with FDA to discuss the new regulatory requirements and to get information regarding what would be necessary to bring Mutual's colchicine drug product into compliance with the statutory and regulatory scheme. (*See id*. at 5.) Because of the wealth of pre-existing information concerning the use of colchicine for the treatment of gout and FDA's prior approval of combination colchicine products like ColBenemid and Col-Probenecid, Mutual discovered that it did not need to submit full NDAs supporting the safety and effectiveness of Colcrys for the treatment of gout. (*See id*. at 5-9.) Instead, Mutual submitted two successive 505(b)(2) NDAs in order to have its 0.6 mg single-ingredient oral colchicine tablet Colcrys approved for two indications: the treatment of acute gout flares and the prophylaxis of gout flares. (*See id*. at 668.)[9] The contents of Mutual's abbreviated new drug applications provide important context for understanding Plaintiffs' challenge to FDA's subsequent approval of Mitigare.

[8] Hikma's generics business apparently operates as West-Ward Pharmaceuticals (*see* http://www.hikma.com/about-hikma/our-businesses.aspx (last visited Jan. 8, 2015)), although the precise contours of the relationship between these two companies is not relevant to the instant dispute. In order to avoid unnecessary confusion, this opinion refers to both of these companies hereinafter collectively, as "West-Ward."

[9] Mutual also sought and obtained FDA approval for Colcrys for treatment of Familial Mediterranean Fever ("FMF"), and received seven years of orphan drug exclusivity for that indication because FMF is a rare disease. (*See* AR at 5-6.) FDA's approval of Colcrys for FMF and Mutual's exclusivity for that indication are not relevant to the instant case.

1. Mutual Relies On ColBenemid, Published Literature, And Its Own Clinical Studies To Support The Colcrys Application For Acute Flares Of Gout

Mutual's first Section 505(b)(2) application for Colcrys, which requested approval of a 0.6 mg single-ingredient oral colchicine tablet for treatment of acute gout flares, identified the combination drug product ColBenemid as the reference listed drug. (*See id* at 7.) In addition, Mutual's application cited FDA's earlier finding that ColBenemid is effective for the chronic treatment of gout, and also relied on published literature about the use of colchicine. Mutual also conducted its own research; specifically, it sponsored two sets of studies that contributed to the existing body of knowledge about the potential toxicity of colchicine.

Mutual's Acute Gout Flare Receiving Colchicine Evaluation trial ("the AGREE trial") was a "randomized, double-blind, placebo-controlled clinical trial" that evaluated "the efficacy, safety, and tolerability of colchicine in patients with an acute gout flare[.]" (*Id*. at 6.) "The AGREE trial was necessary for approval of colchicine for the treatment of acute gout flares because only a single randomized, controlled clinical trial of colchicine in this indication existed in the medical literature." (*Id*. at 22.) The AGREE trial showed that a low-dose regimen of colchicine for the treatment of acute gout flares reduced the number of adverse events that patients experienced but was still as effective at treating gout flares as a higher dose regimen.[10] (*Id*. at 6-7.) This new data "improve[d] the safety profile of colchicine when used to treat acute gout flares"

[10] "The standard (historical) high-dose regimen consisted of 1.2 mg followed by six additional doses of 0.6 mg at hourly intervals, for a total dose of 4.8 mg colchicine. The lower dose regimen consisted of 1.2 mg followed by 0.6 mg in 1 hour, for a total dose of 1.8 mg colchicine." (*See* AR at 6 n.21.)

and permitted Mutual to develop a new, low-dose regimen for the use of colchicine for the treatment of acute gout flares. (*Id*. at 7.)[11]

Mutual also conducted certain drug-drug interaction studies ("DDI studies") comparing colchicine administered alone with colchicine administered in conjunction with other drugs. (*Id*.) Such drugs included cytochrome P4503 ("CYP3A4") inhibitors and Pglycoprotein ("P-gp") inhibitors—pharmaceuticals that can affect the mechanisms that the body uses to metabolize colchicine, and thus were already known to have the potential of leading to toxic colchicine blood levels. (*Id*. at 50, 58-60, 668.) As a result of its DDI studies, Mutual developed a new dosing regimen for concomitant use of Colcrys with certain CYP3A4 inhibitors and P-gp inhibitors. Thus, although the potential for adverse reactions from the interaction of certain drugs with colchicine was already well-known prior to Mutual's research, Mutual's DDI studies "allowed for a more precise quantitative assessment of the interactions." (*Id*. at 668; *see also id.* at 50 (summarizing dose modifications developed by Mutual).)

FDA approved Mutual's 505(b)(2) NDA for Colcrys for the treatment of acute gout flares on July 30, 2009. (*See* AR at 6.) On that same day, based on Mutual's AGREE trial and DDI studies, FDA issued a related drug safety communication for healthcare providers (an "FDA Alert"). *See* FDA, *Information for Healthcare Professionals: New Safety Information for Colchicine (marketed as Colcrys)* (July 30,

[11] Because the AGREE trial was a new clinical investigation essential to the approval of Colcrys for the treatment of acute gout flares, FDA granted Mutual a 3-year period of exclusivity for the treatment of acute gout flares, which expired on July 30, 2012. (*Id*. at 7) *See also* 21 U.S.C. § 355(c)(3)(E)(iii) (FDA may grant a drug sponsor a 3-year period of exclusivity for conducing new clinical investigations essential to the approval of an application).

2009).[12] This FDA Alert informed healthcare professionals of the results of the Mutual colchicine studies, namely that "a substantially lower dose of colchicine was as effective as the traditional higher dose in treatment of acute gout flares" and that colchicine could have dangerous "drug interactions with P-gp inhibitors or strong CYP3A4 inhibitors[.]" (AR at 7.) FDA purportedly took this action to combat "outdated assumptions of what is safe and effective for treatment with oral colchicine" and to ensure that patients would not "suffer from adverse reactions such as severe gastro-intestinal complications—and even death—needlessly." (*Id*. at 8 (internal quotation marks omitted.) The FDA Alert also "referred healthcare professionals to the dosing recommendations and additional drug interaction information in Colcrys product labeling." (*Id*. at 7.)

2. Mutual Relies on ColBenemid and Published Literature To Support The Colcrys Application For Prophylactic Treatment of Gout

Approximately three months after the FDA Alert was issued, on October 16, 2009, FDA approved a second Colcrys application, this time for the prophylaxis of gout flares. (*See id*. at 8.) Unlike Mutual's application for approval of Colcrys for the treatment of acute gout flares, Mutual's application for Colcrys for the prophylaxis of gout flares did not include new studies in support of the safety and efficacy of the drug product. (*Id*.) Instead, Mutual's assertion that Colcrys is a safe treatment for the prophylaxis of gout flares was based on "an assessment of adverse events from the worldwide literature and postmarketing adverse event databases" and "cross-reference to Mutual's earlier colchicine NDAs." (*Id*.) Mutual's assertion that Colcrys is an

[12] Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyinformationforPatientsandProviders/DrugSafetyinfor mationforHeathcareProfessionals/ucm174315.htm.

effective treatment for the prophylaxis of gout flares "was based entirely on the published literature, including published reports of two randomized, controlled trials of colchicine for this indication and the DESI finding for ColBenemid" (*id*. at 22-23 (footnote omitted)).

3. FDA Takes Enforcement Action Against Unapproved Oral Colchicine Products Because Their Labels Do Not Reflect The Most Current Data

On September 30, 2010—nearly one year after Colcrys was approved for prophylaxis of gout flares—"FDA announced its intention to take enforcement action against unapproved single-ingredient oral colchicine products and persons who manufacture or cause the manufacture of such products or their shipment in interstate commerce." (*Id*. at 9.) This action was part of the broader initiative that the agency had launched in 2006 against unapproved marketed drugs generally, and with respect to colchicine products in particular, FDA remarked that "the labeling for unapproved single-ingredient oral colchicine products listed with FDA . . . does not reflect the most current data regarding the safety and effectiveness of single-ingredient oral colchicine." *See Single-Ingredient Oral Colchicine Products; Enforcement Action Dates; Notice*, 75 Fed. Reg. 60768 at 60769-70 (effective October 1, 2010); *see also* FDA News Release, "FDA orders halt to marketing of unapproved single-ingredient oral colchicine" (Sept. 30, 2010).

Notably, the agency expressed a particular concern with how the labels of unapproved colchicine products dealt with the use of colchicine for the treatment of acute gout flares and potential drug-drug interactions—the two areas that Mutual had studied and had specifically addressed in the Colcrys label. Unlike Colcrys, the labels of unapproved colchicine products generally used vague warnings suggesting

"avoidance when possible and caution when necessary, with vigilant monitoring of clinical signs of toxicity." (AR at 668.) By contrast, consistent with the findings of Mutual's DDI studies and AGREE trial, the Colcrys label contained both: (1) a two-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 (*see* Compl. Ex. 5 at 5-6), and (2) a low dose regimen of colchicine for treatment of acute gout flares that occur while colchicine is already being used to treat prophylaxis (*see id*. at 3). FDA suggested that it was important that similar information appear on the labels of all colchicine products, calling Mutual's findings about lower dosing for acute gout flares "the standard of care" at the time, and also noting that "awareness regarding colchicine interactions may not be widespread in the healthcare community." 75 Fed. Reg. 60769.

D. FDA's Approval Of Mitigare (A Colchicine Capsule)

West-Ward removed its unapproved single-ingredient 0.6 mg colchicine tablet from the market in response to FDA's enforcement announcement, just as Mutual had done. (AR at 50.) West-Ward had been marketing its 0.6 mg single-ingredient oral colchicine tablet since the early 1970s. (*Id.*) In an attempt to comply FDA's new approval scheme and announced enforcement measures, West-Ward submitted a Section 505(b)(2) application to FDA for approval of its pre-existing colchicine tablet. (*Id*. at 50-51.) Before filing its application, however, West-Ward specifically inquired of FDA whether the agency would entertain a 505(b)(2) application for a colchicine tablet that referenced and relied upon Col-Probenecid, rather than Mutual's recently-approved Colcrys, and the agency answered in the affirmative. (*See id.* at 6.) It is undisputed that West-Ward wanted to cite Col-Probenecid instead of Colcrys because, unlike

Colcrys, Col-Probenecid is not tied to any patents that would require West-Ward to submit a Paragraph IV certification that would delay the approval and re-marketing of West-Ward's colchicine product.

West-Ward filed the aforementioned Section 505(b)(2) application for approval of a colchicine tablet that referenced Col-Probenecid in August 2010. (*See* AR at 50.) Although FDA's new drug approval process is confidential, Mutual learned of West-Ward's application through public sources while approval was pending. (Compl., Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ (D.D.C. Oct. 6, 2014), ECF No. 1, ¶ 35.)

1. Mutual Files A Citizen Petition Protesting West-Ward's Application And FDA Responds

On November 26, 2010, Mutual filed a "citizen petition" with FDA regarding the agency's requirements for ANDAs and Section 505(b)(2) NDAs for colchicine tablets.[13] Mutual specifically requested that FDA take, or refrain from taking, a number of actions; as relevant here, Mutual asked the agency to:

(1) "[r]efrain from filing or approving any application for a 0.6 mg oral colchicine tablet with a proposed indication already approved for Colcrys (*i.e.*, a "duplicate" of Colcrys) that is not submitted as an ANDA";

(2) "[r]efrain from filing or approving any ANDA or 505(b)(2) application for a single-ingredient oral colchicine product that does not reference Colcrys and include certifications to the patents listed in FDA's [Orange Book] for Colcrys;" and

(3) "[r]equire the labeling for any single-ingredient oral colchicine product to include all information related to drug-drug interactions that is in the Colcrys labeling,

[13]A citizen petition is a written request that any interested person can file with FDA, asking the agency to take, or refrain from taking, any form of administrative action. *See* 21 C.F.R. §§ 10.25(a), 10.30.

including relevant dose adjustments needed to prevent unnecessary toxicity[.]" (AR at 1.) In other words, Mutual asked FDA to mandate that every single-ingredient oral colchicine product submitted to the agency for approval both reference Colcrys and have the same safety information and dose adjustments that are on Colcrys's label; and also that FDA reject any application for a drug product exactly like Colcrys that is submitted through the 505(b)(2) pathway.

On May 25, 2011, FDA responded to Mutual's Citizen Petition, granting the petition in part and denying it in part. (*See id*. at 2.) For present purposes, FDA made three significant decisions. First, the Colchicine Citizen Petition Response sustained Mutual's objections to West-Ward's 505(b)(2) application for a 0.6 mg single-ingredient colchicine tablet that was identical to Colcrys. FDA acknowledged that it had previously advised West-Ward that West-Ward could submit an application for its 0.6 mg single-ingredient colchicine tablet via the 505(b)(2) pathway and without referencing Colcrys, but admitted in the Response that the agency had been "incorrect" about that, and added that "FDA regrets that [] advice to West-Ward." (*Id*. at 17.) Thus, FDA granted Mutual's request that the agency require any application for a single-ingredient oral colchicine product that was identical to Colcrys "be submitted as an ANDA that cites Colcrys as the RLD and complies with applicable regulatory requirements." (*Id*. at 2-3.) FDA also stated that the West-Ward application needed to be withdrawn and resubmitted as an ANDA (*see id*. at 11-16).

Second, FDA's Citizen Petition Response addressed Mutual's broader contention that *any* single-ingredient colchicine product—not just a 0.6 mg tablet such as the one submitted by West-Ward—"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." (*Id*. at 3.) FDA denied this request. (*See id*.) The agency explained that a drug product that differs from Colcrys in one of the above listed ways is *not* a "duplicate" of Colcrys and therefore presents a different set of circumstances than West-Ward's admittedly incorrect 505(b)(2) application for a 0.6 mg single-ingredient oral colchicine tablet that did not reference Colcrys.[14] (*See id*. at 12-13.) FDA stressed that, although requiring duplicate products to be approved through the ANDA pathway "ensures that duplicate products are marketed with the same or similar labeling that FDA has determined contains the scientific information necessary for the safe and effective use" (*id*. at 13), a 505(b)(2) NDA must directly demonstrate that the proposed drug product is safe and effective. (*See id*. at 3 (noting that "any 505(b)(2) application for a proposed single-ingredient colchicine product must meet the statutory approval standard for safety and effectiveness").) The agency also remarked that, "in 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." (*Id*. at 21.) Thus, although FDA promised that it would reject an application for a duplicate of Colcrys that did not reference Colcrys, FDA also anticipated that the agency might approve a single-ingredient oral colchicine product that did not cite Colcrys, so long as the new drug product differed from Colcrys in some

[14] Here, "duplicate" is a term of art that refers to a drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug. *See* Abbreviated New Drug Application Regulations; Proposed Rule, 54 Fed. Reg. 28872 at 28877 (July 10, 1989).

way and the new drug product's 505(b)(2) application made the requisite showing of safety and effectiveness.

Third, FDA's Citizen Petition Response described what type of information FDA would require for the label of a single-ingredient oral colchicine product. With respect to label information about concomitant use of colchicine with other drugs, FDA commented that "Mutual's drug-drug interaction studies [had] provided new, quantitative information about the extent of changes in exposure that can occur with co-administration of certain drugs with colchicine." (*Id.* at 19.) Thus, the label "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." (*Id*. at 3.) As for the use of colchicine to treat the acute flares of patients who were already taking colchicine for prophylaxis, FDA stated that "the labeling for a single-ingredient colchicine product seeking approval for prophylaxis of gout flares must inform healthcare providers that the lower dose colchicine regimen evaluated in the AGREE trial is adequate to treat an acute gout flare that may occur during chronic colchicine use[.]" (*Id*. at 3.)

2. <u>FDA Approves Mitigare Capsule For Prophylaxis Of Gout Flares Based On Col-Probenecid, Published Literature, and West-Ward's Own Studies</u>

After FDA determined that it was unacceptable for West-Ward to submit a Section 505(b)(2) application for a colchicine tablet that was a duplicate of Colcrys, as explained above, West-Ward reformulated its product, and submitted a new 505(b)(2) application for a colchicine *capsule* named Mitigare. West-Ward's application for Mitigare relied on published literature about colchicine, FDA's findings of safety and effectiveness from Col-Probenecid, and new clinical pharmacology studies West-Ward

conducted. (*See* AR at 108.) This application differed from West-Ward's earlier application for a single-ingredient colchicine product in at least two significant ways.

First, Mitigare is a capsule, not a tablet. Like Colcrys, Mitigare contains 0.6 mg of colchicine administered orally, but the difference in dosage form means that Mitigare is not a duplicate of Colcrys, and as a result, FDA permitted West-Ward to file its application for Mitigare using the 505(b)(2) pathway rather than the ANDA pathway. (*See* Ex. 11 to Takeda Compl., ECF No. 1-1, at 217-32, FDA Ctr. for Drug Evaluation & Research, Guidance for Indus.: Appls. Covered By Sec. 505(b)(2), Draft Guidance (Oct. 1999) at 6 (noting that "[a]n application that is a duplicate of a listed drug and eligible for approval under section 505(j)" "can't be submitted as 505(b)(2) application").)

Second, West-Ward conducted new DDI studies to support its application. In an effort to produce a single-ingredient oral colchicine product that did not reference Colcrys or rely upon Mutual's data, West-Ward commenced a development program that FDA recommended in which West-Ward sponsored DDI studies similar to Mutual's but involving a different set of CYP3A4 and P-gp inhibitor drugs. (AR at 118, 669.) Per FDA's advice, West-Ward chose to study the same classifications of drugs that Mutual studied; however, contrary to expectations, the results of West-Ward's studies differed substantially from the results of Mutual's studies. (*See id*. at 669-70.) Mutual's studies had indicated that colchicine dosing regimens should be modified when colchicine is co-administered with certain types of drugs, but West-Ward's results indicated that dose modifications are "not warranted" when 0.6 mg colchicine is administered concomitantly with certain CYP3A4 inhibitors and P-gp inhibitors. (*Id*. at

670.) When West-Ward submitted its research as part of the Mitigare application, FDA wrestled with these unexpected results, comparing Mutual's data with West-Ward's data and attempting to understand the differing results. (*See id*. at 667-711.)

FDA ultimately reached the conclusion that Mitigare is safe and effective for the prophylaxis of gout, and approved West-Ward's 505(b)(2) application on September 26, 2014. (*See id*. at 28.) As approved, Mitigare not only differs from Colcrys in dosage form, it also has a substantially different label than Colcrys. In contrast to the Colcrys label, the Mitigare label does not include the lower dose colchicine regime for the treatment of acute gout flares that Mutual evaluated in its AGREE trial; rather, the Mitigare label states under the "[l]imitations of use" section that "[t]he safety and effectiveness of Mitigare for acute treatment of gout flares during prophylaxis has not been studied." (*id*. at 32 (Mitigare label)). Furthermore, instead of the detailed dose modifications for preventing drug-drug interaction toxicity that the Colcrys label contains, the Mitigare label warns generally that patients taking certain drugs in combination with Mitigare should avoid the combination entirely, or if avoidance is not possible, 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." (AR at 141 (citation omitted).)

3. West-Ward Launches Mitigare, Alerting Takeda To The Existence Of Mitigare

FDA's evaluation of West-Ward's application for Mitigare was undertaken confidentially, in accordance with FDA rules and regulations. *See* 21 C.F.R. § 314.430(b) ("FDA will not publicly disclose the existence of an application or abbreviated application before an approval letter is sent to the applicant under

§ 314.105 or tentative approval letter is sent to the applicant under § 314.107[.]"). Moreover, because West-Ward neither cited Colcrys as the RLD nor certified to any Colcrys patents in West-Ward's 505(b)(2) application for Mitigare, West-Ward did not inform Takeda of West-Ward's application for Mitigare. Consequently, Plaintiffs did not know about West-Ward's application for Mitigare until September 30, 2014, when West-Ward issued a press release regarding FDA's approval of its new single-ingredient colchicine product. (*See* Confidential Decl. Matthew Woods, Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ, ECF No. 3-6 ¶ 33.) Moreover, Takeda only discovered that West-Ward intended to market an authorized generic version of Mitigare that will compete with—and cost less than—Takeda's Colcrys, on October 1, 2014. (*See id*. ¶ 34.)

E. Procedural History

On October 6, 2014, Takeda filed a two-count complaint and a Motion for a Preliminary Injunction against Defendants Burwell and Hamburg. (*See* Compl., Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ (D.D.C. Oct. 6, 2014), ECF No. 1 ("Takeda Compl."); Mot. for TRO or Prelim. Inj., Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ (D.D.C. Oct. 8, 2014), ECF No. 9, *see also* Mem. Supp. Pl.'s Confidential Mot. for TRO or Prelim. Inj., Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ (D.D.C. Oct. 8, 2014), ECF No. 10 ("Takeda PI Mem.").) In its complaint, Takeda alleges that FDA acted wrongfully in three respects: (1) "FDA acted arbitrarily and capriciously in approving [West-Ward's] Section 505(b)(2) application for Mitigare without requiring the label to contain critical safety information that FDA previously stated was necessary for single-ingredient oral colchicine products[;]" (2) "FDA's approval of [West-Ward's] application for Mitigare

was unlawful, arbitrary and capricious because, as approved, Mitigare is not safe in light of the defects in its label[;]" and (3) "FDA's failure to require [West-Ward] to reference Takeda's own colchicine drug, Colcrys, in its application interfered with Takeda's rights to participate in the administrative process, including the Paragraph IV certification process under Hatch Waxman and the Citizen Petition process." (Takeda Compl. ¶ 1.)

Takeda initiated a patent infringement action against West-Ward in the United States District Court for the District of Delaware shortly before it brought this action against FDA. (*See* Compl., Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp., No. 14-1268-SLR (D. Del. Oct. 3, 2014), ECF No. 1.) On October 9, 2014, the Delaware court entered a Temporary Restraining Order enjoining West-Ward from marketing Mitigare pending further proceedings in the patent litigation. (*See* Memorandum Order, Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp., No. 14-1268-SLR (D. Del. Oct. 9, 2014, ECF No. 21.) The Delaware court eventually denied Takeda's Motion for a Preliminary Injunction, but "given the significance of this dispute to both parties" issued an order maintaining the status quo—that is, prohibiting West-Ward from marketing Mitigare—pending Takeda's appeal of that court's decision regarding the preliminary injunction. (Memorandum Opinion at 16, Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp., No. 14-1268-SLR (D. Del. Nov. 4, 2014), ECF No. 78, 2014 WL 5088690; *see also* Order, Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp., No. 14-1268-SLR (D. Del. Nov. 4, 2014), ECF No. 79.)

Meanwhile, in the instant District of Columbia case, West-Ward moved to intervene in Takeda's suit against FDA, and this Court granted that request. (*See*

Unopposed Mot. to Intervene, Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ (D.D.C. Oct. 9, 2014), ECF No. 11; Minute Entry dated Oct. 9, 2014, Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ.) West-Ward and the Government then filed oppositions to Takeda's Motion for a Preliminary Injunction. (*See* Hikma and West-Ward's Opp'n to Mot. for TRO ("West-Ward Opp. Mem."), Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ (D.D.C. Oct. 17, 2014), ECF No. 16; Burwell and Hamburg's Resp. to Mot. for TRO ("FDA Opp. Mem."), Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ (D.D.C. Oct. 17, 2014), ECF No. 15.) Takeda field a reply on October 20, 2014. (*See* Reply to Opp'n to Mot. for TRO ("Takeda Reply Mem."), Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ (D.D.C. Oct. 20, 2014), ECF No. 21.)

On November 4, 2014, this Court heard argument from Takeda, FDA, and West-Ward on Takeda's Motion for a Preliminary Injunction. (*See* Minute Entry dated Nov. 4, 2014, Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ). However, in light of the stay that was issued in the Delaware patent litigation, this Court consolidated Takeda's Motion for a Preliminary Injunction with the resolution of the merits of Takeda's complaint and, with Takeda's consent, construed the merits arguments in Takeda's preliminary injunction motion as a motion for summary judgment. (*See* Order, Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ (D.D.C. Nov. 5, 2014), ECF No. 40.) The parties subsequently filed supplemental briefs on Takeda's converted motion. (*See* Burwell and Hamburg's Supplemental Mem. ("FDA Suppl. Mem."), Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ (D.D.C. Nov. 14, 2014), ECF No. 43; Takeda's Supplemental Mem. ("Takeda Suppl. Mem."), Takeda

Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ (D.D.C. Nov. 14, 2014), ECF No. 44; Hikma and West-Ward's Supplemental Mem., ("West-Ward Suppl. Mem."), Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ (D.D.C. Nov. 14, 2014), ECF No. 45.)

On the same day that this Court heard argument on Takeda's then-pending preliminary injunction motion (November 4, 2014), Elliott Associates, L.P., Elliott International, L.P., and Knollwood Investments, L.P. (collectively, "Elliott") filed a two-count complaint against Defendants Burwell and Hamburg that is substantially similar to Takeda's action. (*See* Compl. Elliott Assocs. v. Burwell, No. 14-1850-KBJ (D.D.C. Nov. 4, 2014), ECF No. 1 ("Elliott Compl.").) Elliott "owns a legally-enforceable right tied to the Colcrys patents to receive a percentage of the royalties from the sale of Colcrys," and because Elliott expects that Mitigare will compete directly with Colcrys, these plaintiffs allege that FDA's failure to require West-Ward to certify to the Colcrys patents has injured them. (Elliott Compl. ¶ 7.) The Elliott complaint specifically alleges that FDA acted wrongfully in two respects: (1) that "FDA's decision to approve Mitigare without requiring that [West-Ward] certify to the patents covering the use of colchicine for the prophylaxis of gout flares violates the plain text of Section 505(b)(2)(A) of the FDCA[;]" and (2) that "FDA acted in an arbitrary and capricious manner by approving [West-Ward's] 505(b)(2) application without requiring a certification as to the Colcrys patents." (*Id*. ¶ 9-11.) Elliott filed a motion for summary judgment on November 17, 2014. (*See* Mot. for Summ. J, Elliott Assocs. v. Burwell, No. 14-1850-KBJ (D.D.C. Nov. 17, 2014), ECF No. 14, *see also* Pl.'s Mem. Supp. Mot. for Summ. J., Elliott Assocs. v. Burwell, No. 14-1850-KBJ

(D.D.C. Nov. 17, 2014), ECF No. 14-1 ("Elliott MSJ Mem.").) Just as they had in *Takeda v. Burwell*, Hikma and West-Ward moved to intervene in *Elliott v. Burwell*. (*See* Consent Mot. to Intervene, Elliott Assocs. v. Burwell, No. 14-1850-KBJ (D.D.C. Nov. 18, 2014), ECF No. 47.) This Court granted the motion. (*See* Minute Entry dated Nov. 21, 2014, Elliott Assocs. v. Burwell, No. 14-1850-KBJ.)

In light of the overlap between the parties, facts, and allegations in *Takeda v. Burwell* and *Elliott v. Burwell*, this Court that the two cases should be considered in tandem. (*See* Minute Entry dated Nov. 18, 2014, Elliott Assocs. v. Burwell, No. 14-1850-KBJ.) On November 19, 2014, this Court held a second motions hearing in which the parties in both cases participated. (*See* Minute Entry dated Nov. 19, 2014, Takeda Pharms. U.S.A., Inc. v. Burwell, No. 14-1668-KBJ.) After the hearing, West-Ward and FDA filed cross-motions for summary judgment in *Elliott v. Burwell*. (*See* Cross Mot. for Summ. J. by Hikma and West-Ward, Elliott Assocs. v. Burwell, No. 14-1850-KBJ (D.D.C. Dec. 9, 2014), ECF No. 60; Mem. in Opp. by Hikma and West-Ward, Elliott Assocs. v. Burwell, No. 14-1850-KBJ (D.D.C. Dec. 9, 2014), ECF No. 61 ("West-Ward XMSJ Mem."); Cross Mot. for Summ. J. by Burwell and Hamburg ("FDA XMSJ Mem."), Elliott Assocs. v. Burwell, No. 14-1850-KBJ (D.D.C. Dec. 9, 2014), ECF No. 62; Mem. in Opp by Burwell and Hamburg, Elliott Assocs. v. Burwell, No. 14-1850-KBJ (D.D.C. Dec. 9, 2014), ECF No. 63 ("FDA XMSJ Mem.").) Elliott filed a reply to both Cross-Motions on December 13, 2014. (*See* Reply to Opp'n and Cross Mot. for Summ. J. ("Elliott MSJ Reply Mem."), Elliott Assocs. v. Burwell, No. 14-1850-KBJ (D.D.C. Dec. 13, 2014), ECF No. 64.) The motions for summary judgment in *Takeda v. Burwell* and *Elliott v. Burwell* are now ripe.

II. LEGAL STANDARDS

Under Federal Rule of Civil Procedure 56, summary judgment is appropriate when the moving party demonstrates "that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56. However, in a case involving review of final administrative action—such as FDA's approval of a new drug—the standard set forth in Rule 56 does not apply. *See, e.g.*, *ViroPharma, Inc. v. Hamburg*, 916 F. Supp. 2d 76, 79 (D.D.C. 2013). Instead, "FDA's administrative decisions are subject to review under the Administrative Procedure Act ('APA'), 5 U.S.C. § 706, which requires the reviewing court to set aside an agency action that is 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.'" *ISTA Pharm., Inc. v. FDA*, 898 F. Supp. 2d 227, 230 (D.D.C. 2012). "Summary judgment thus serves as a mechanism for deciding, as a matter of law, whether the agency action is supported by the administrative record and is otherwise consistent with the APA standard of review." *Hill Dermaceuticals, Inc. v. FDA*, No. 11-1950, 2012 WL 5914516, at *7 (D.D.C. May 18, 2012) (citing *Richard v. INS*, 554 F.2d 1173, 1177 & n. 28 (D.C. Cir. 1977)); *see also Am. Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1083-84 (D.C. Cir. 2001) (collecting cases).

In reviewing agency action, a court must be mindful of the division of labor between the court and the agency. "Under the APA, it is the role of the agency to resolve factual issues to arrive at a decision that is supported by the administrative record, whereas the function of the district court is to determine whether or not as a matter of law the evidence in the administrative record permitted the agency to make the decision it did." *Hi-Tech Pharmacal Co. v. FDA*, 587 F. Supp. 2d 13, 18 (D.D.C. 2008) (internal quotation marks and citation omitted). Accordingly, a reviewing court

cannot "substitute its judgment for that of the agency," *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983), especially when the agency's scientific expertise informs its judgment. *See Balt. Gas & Elec. Co. v. Natural Res. Def. Council, Inc.*, 462 U.S. 87, 103 (1983) (holding that "[w]hen examining . . . [a] scientific determination . . . a reviewing court must generally be at its most deferential"). Moreover, given that "[t]he scope of review under the 'arbitrary and capricious' standard is narrow[,]" *State Farm*, 463 U.S. at 43, the agency action under review is "entitled to a presumption of regularity[,]" *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 415 (1971), *overruled on other grounds by Califano v. Sanders*, 430 U.S. 99 (1977). In sum, the court performs "only the limited, albeit important, task of reviewing agency action to determine whether the agency conformed with controlling statutes[,]" *Balt. Gas*, 462 U.S. at 97, and/or whether the agency has committed "a clear error of judgment[,]" *Overton Park*, 401 U.S. at 416.

III. DISCUSSION

Although the instant cross-motions for summary judgment focus on the alleged impropriety of one agency action—FDA's approval of Mitigare—Plaintiffs make myriad arguments in an attempt to support their claim that FDA's approval of that drug product was wrongful and should be rescinded. First, both Takeda and Elliott steadfastly maintain that FDA should not have approved Mitigare without requiring West-Ward to certify to the Colcrys patents that cover the use of colchicine for the prophylaxis of gout flares, with Takeda asserting that the agency relied on Colcrys's data to approve Mitigare and thus FDA's failure to require West-Ward to reference Colcrys and certify to the Colcrys patents violated the agency's own procedural rules

(*see* Takeda Reply Mem. at 19-22; Takeda Suppl. Mem. at 6-13), and Elliott arguing additionally that the agency's failure to require West-Ward to certify to the Colcrys patents without regard to any reliance on Colcrys contravened both the agency's longstanding policies and the FDCA itself (*see* Elliott MSJ Mem. at 23-46).[15] In addition, Takeda takes issue with Mitigare's label, arguing that "[t]he Mitigare label contains neither the FDA-approved low-dose-treatment notation for acute gout nor the drug-drug interaction dosing adjustments, both of which FDA expressly required in light of the severe safety concerns it identified during the Colcrys review process." (Takeda PI Mem. at 32 (citation omitted).) Consequently, Takeda contends that Mitigare is unsafe as labeled, and also that FDA's approval of Mitigare constitutes an unreasoned change in the agency's position regarding the requirements for the labeling of single-ingredient oral colchicine products. (*See id*. at 26-36.) Takeda also argues that "FDA's failure to enforce its own labeling requirements allowed [West-Ward] to circumvent the statutory directive that it file a Paragraph IV certification to Takeda's patents[.]" (*Id*. at 36.)

For the reasons explained below, this Court concludes that Plaintiffs are wrong to characterize FDA's actions with respect to Mitigare as unauthorized, unsafe, or unreasoned; to the contrary, it is clear on the record presented that FDA's approval of Mitigare was consistent with the FDCA, the regulations the agency has promulgated pursuant to the FDCA, the Citizen Petition Responses FDA has issued, and the policies and practices under which the agency operates. Furthermore, the record clearly reveals the reasonableness of FDA's expert determination that Mitigare is safe and effective as

[15] Citations to documents that the parties have filed refer to the page numbers that the Court's electronic filing system assigns.

labeled, and it supports the agency's conclusion that Mitigare's labeling best reflects current scientific information regarding the risks and benefits of Mitigare—a conclusion that, in any event, is entitled to a high degree of deference. Consequently, Plaintiffs have failed to establish that summary judgment should be entered in their favor on their APA claims, and this Court finds that Defendants are entitled to summary judgment as a matter of law.

A. FDA's Approval Of Mitigare Without A Colcrys Reference And Related Certifications To The Colcrys Patents Did Not Violate The Agency's Rules Or The FDCA

Both Plaintiffs contend that, when FDA approved Mitigare without a Paragraph IV certification to the Colcrys patents, FDA permitted West-Ward to "circumvent" the agency's own Hatch-Waxman directives regarding the filing of patent certifications, in a manner that was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law. (*See* Takeda PI Mem. at 36; Takeda Compl. ¶¶ 1, 56; Elliott MSJ Mem. at 29; Elliott Compl. ¶ 14); *see also* 5 U.S.C. § 706(2)(A). It bears noting at the outset that the assertion that FDA should have required West-Ward to reference Colcrys and to certify to the Colcrys patents is, from a broad perspective, the same argument that Takeda's predecessor Mutual made to FDA in its 2010 Citizen Petition (*see supra* Part I.D.1), when Mutual specifically asked that the agency refrain from approving any future Section 505(b)(2) application for a single-ingredient oral colchicine product that does not reference Colcrys and include certifications to the Colcrys patents. (*See* AR at 1.) As explained above, FDA specifically rejected that request in its Colchicine Citizen Petition Response, stating, *inter alia*, that a Section 505(b)(2) application for a single-ingredient oral colchicine product might not need to cite Colcrys as its reference listed drug if the new drug does not share the same dosage form. (*See* AR at 3; *see also supra*

Part I.D.1.) The agency also emphasized that "[w]hether another 505(b)(2) application for a single-ingredient colchicine product that does not cite Colcrys as a listed drug could ever be appropriate will depend on the facts and circumstances of the particular application[.]" (AR at 21.)

Plaintiffs argue now that the facts and circumstances of Mitigare's approval are such that the agency should have required a Colcrys reference and patent certifications, and that FDA arbitrarily and capriciously failed to do so. To be specific, Takeda asserts that FDA's refusal to make West-Ward reference Colcrys and certify to the Colcrys patents violated two of the agency's "procedural requirements": (1) the requirement that a Section 505(b)(2) applicant reference another product if the agency itself relies on studies or data relating to that other product in approving the applicant's application, and (2) the requirement that a Section 505(b)(2) applicant choose the "most appropriate" listed drug to be its reference drug. (Takeda Reply Mem. at 17; *see also id*. at 16-22.) Elliott makes the slightly different argument that FDA not only violated the agency's own policies, its actions also breached the FDCA itself, which, according to Elliott, requires a Section 505(b)(2) applicant to certify to all method-of-use patents that claim a use for the drug substance for which the applicant is seeking approval. (*See* Elliott MSJ Mem. at 23-46). As explained below, this Court discerns no basis in law or fact for Plaintiffs' insistence that FDA was legally required to force West-Ward to reference Colcrys and to certify to the Colcrys patents under the circumstances presented here. Consequently, this Court cannot accept Plaintiffs' arguments that FDA arbitrarily and capriciously violated any such requirements when it approved West-Ward's application for Mitigare.

1. FDA's Procedural Rules Did Not Require West-Ward To Reference Colcrys Because West-Ward Did Not Rely On Colcrys Data To Support West-Ward's Application For FDA Approval Of Mitigare

Takeda appears to accept that reliance on the studies of another drug product is a necessary prerequisite to the obligation of a Section 505(b)(2) applicant to certify to that product's patents, and it vigorously asserts that the obligation to certify to the Colcrys patents was triggered here under FDA's own rules because "FDA relied repeatedly and extensively upon Colcrys's safety and efficacy data in approving Mitigare." (Takeda Suppl. Mem. at 5.) As Takeda puts it, "the triggering event for identifying a reference drug in a 505(b)(2) application and certifying to patents is not based solely the *applicant's* actions" (*id.* at 6 (emphasis in original)), and, as Takeda views the record, FDA's actions with respect to the approval of Mitigare clearly involved the degree of reliance on the Colcrys data that is necessary to require FDA to make West-Ward certify to the Colcrys patents. (*See id*. at 5 ("Colcrys was referenced *246 times* in the Mitigare administrative record, and FDA expressly relied on Colcrys data to support findings of Mitigare's safety and efficacy." (emphasis in original)).) Boiled to bare essence, Takeda's reliance argument has two major corollaries: (1) that, under FDA's rules, "[t]he ultimate reference and certification obligations depend on whether *FDA* relies on other drug studies or data" regardless of whether the Section 505(b)(2) applicant does so (*id*. at 6 (emphasis in original)), and (2) that the instant administrative record shows that "FDA explicitly referenced and relied on the Colcrys data—over and over and over again—in approving Mitigare." (Takeda Reply Mem. at 19.) This Court finds that Takeda is wrong on both counts.

a. No FDA Policy Establishes That FDA's Reliance—As Opposed To That Of The Section 505(b)(2) Applicant—Gives Rise To Patent Certification Obligations

First of all, the contention that, under established agency policy, the patent certification requirement is triggered by *the agency's* reliance on the investigations underlying another drug product is entirely unsupported. (*See* Takeda Suppl. Mem. at 7 (maintaining that "[i]f FDA relied on Colcrys to support the approval of Mitigare, [West-Ward] was required to reference Colcrys and certify to its patents").) Takeda does not cite to any one regulation or clearly applicable agency statement to bolster its assertions in this regard; instead, Takeda points to various sources—*e.g.*, section 505(b)(2) of the FDCA, a few lines from FDA's implementing regulations, a case that settled, and selective quotations from Citizen Petition Reponses (*see* Takeda Suppl. Mem. at 8-9)—to cobble together a legal argument that, in essence, asks this Court to apply its own logic to conclude that FDA's reliance matters, when, as explained below, this conclusion is hardly logical.

The key to understanding why Takeda's agency-reliance argument fails is recognizing its linchpin: the proposition that, without "a right of reference or use," FDA lacks the authority to review or access third-party data from a previously approved new drug application when it is evaluating a Section 505(b)(2) new drug application. (*See* Takeda Suppl. Mem. at 9 ("FDA's use of third-party data [to consider and approve a 505(b)(2) application] *without a right of reference* would trigger the 505(b)(2) obligations." (emphasis added)); *see also id.* ("If there is *no right of reference or use*, FDA does not have carte blanche to consult or rely on third-party data that might be relevant to an application without requiring the applicant to reference and certify to the relevant patents." (emphasis altered)).) As Takeda explains it, in the absence of a right

of reference or use, FDA is not entitled "to refer to data from a previously approved application during the review of another party's 505(b)(2) application" (*id*. at 9), and it is precisely because of the agency's limited authority to access such data that, if the agency *does* undertake to consult third-party data as part of its evaluation of a Section 505(b)(2) application, the agency must require the applicant to certify to the data owner's patents. (*See id.* at 10 (asserting that, "where the [505(b)(2)] applicant fails in its duty to identify a referenced drug, to the extent *FDA* relies on that drug's studies or data, FDA must require that applicant to reference the drug and certify to its patents" (emphasis in original); *see also* Mot. Hr'g Tr. Nov. 19, 2014 (hereinafter, "MSJ Mot. Hr'g Tr.") 26:24 (emphasizing that "[t]he data that Takeda and Mutual submitted is propriety"); *id*. at 28:12-20 (arguing that "[w]hen FDA takes it upon itself to do an applicant's work for it and opens that locked file drawer and pulls out the Mutual file and consults the Mutual studies and uses the Mutual data and combines them with [West-Ward]'s data in order to reach certain conclusions about the safety and effectiveness of [West-Ward's] drug, then . . . there's an obligation that adheres in the Hatch-Waxman Act for FDA to go back to [West-Ward] and say, 'Before we go further you need to reference the right drug'").) Of course, FDA's purported obligation to require certification to a third-party data owner's patents when the agency relies on third-party data without a right of reference *assumes* that FDA cannot otherwise rely on such data—a contention that Takeda repeatedly makes—but this critical limitation simply does not appear in any of the sources that Takeda cites.

Specifically, although Congress uses the phrase "right of reference or use" in 21 U.S.C. § 355(b)(2), that statutory section expressly applies only to the Section

505(b)(2) applicant, and pertains only to what application materials such sponsor is required to submit; Takeda fails entirely to explain its suggestion that this statutory language can somehow be read to bind *FDA* in its consideration of data pertinent to a submitted application. (*See* Takeda Suppl. Mem. 8.) And just as the statute says nothing about the circumstances under which FDA can, or cannot, consult third-party data when it makes a scientific determination regarding whether or not to approve a Section 505(b)(2) application, the "right of reference" definition that the agency provides in 21 C.F.R. § 314.3 is similarly silent on the issue of whether the agency itself needs such a "right" before it can "refer to data from a previously approved application during the review of another party's 505(b)(2) application[,]" as Takeda maintains. (Takeda Suppl. Mem. at 9.)

Pfizer Inc. v. FDA, No. 03- 2346 (D.D.C. filed Nov. 13, 2003) also fails to shed any light on the subject. Takeda cites *Pfizer* as an example of a circumstance in which "FDA was sued for improperly referencing third-party data to approve a 505(b)(2) application submitted by Dr. Reddy's Labs for the drug amlodipine maleate." (Takeda Suppl. Mem. at 9.) What Takeda does *not* explain in its brief is that the court in *Pfizer* never reached any legal conclusion regarding whether the agency has a blanket policy of prohibiting its employees from consulting third-party data without a right of reference or use—the case was ultimately dismissed—and, indeed, it is highly likely that FDA requested the stay and dismissal based on doubts about the *particular* studies its reviewer relied upon in that case and not on the basis of some unstated agency policy prohibiting unauthorized reliance on third-party studies entirely. *See* Pfizer Inc. v. FDA, No. 03- 2346 (D.D.C. Nov. 13, 2003), ECF No. 1, Compl. ¶ 15-37, *see also id*.

¶ 36 (alleging that "there could be no reasonable *scientific* basis to rely on data contained in Pfizer's NDA for Norvasc to approve Reddy's drug" (emphasis added)). In other words, although FDA may have seen fit, under the circumstances presented in *Pfizer*, to "reevaluate whether the approval of the NDA . . . was based upon data from appropriate sources" (Takeda Suppl. Mem. at 9 (alteration in original) (internal quotation marks and citation omitted)), that case by no means establishes an FDA policy that it is inappropriate for the agency to rely on any data or information from third-party sources without a right of reference, as Takeda maintains.[16]

This Court is also at a loss to ascertain how any supposed "right of reference or use" requirement for the agency's consideration of third-party data (the flip side of Takeda's assertion that the agency cannot proceed to rely on third-party data without such a right) would work, as a practical matter. Given the confidential nature of the Section 505(b)(2) application process, it makes little sense to suggest, as Takeda does, that FDA cannot consider the previously-submitted safety and effectiveness data of third-party drug sponsors as part of its review of a Section 505(b)(2) application without securing the data owner's permission. (*Cf.* MSJ Mot. Hr'g Tr. at 23:22-24:17 (arguing that, "when FDA looks at [a 505(b)(2)] application and concludes that it is going to need to go to a different file and pull a different file out of the drawer and

[16] Takeda's attempt to find an FDA policy regarding its need for a "right of reference or use" in a citizen petition response that the agency issued in in 2007 is likewise unavailing. Takeda asserts that "FDA has previously acknowledged that the 'right of reference or use' permits FDA to refer to data from a previously approved application during the review of another party's 505(b)(2) application," Takeda Suppl. Mem. at 9 (citing Ltr. from Randall W. Lutter, Assoc. Comm'r for Pol'y and Planning, FDA, to Jeffrey Chasnow and Kelly Falconer, Pfizer, Inc., (May 18, 2007) (responding to Citizen Petition Dkt. Nos. 2007P-0110/CP1 and 2007P-0111/PSA1); however, FDA made this statement in the context of a dispute between two private parties over the continued validity of a right of reference that one of the parties had previously secured from the other, and when the statement is read in context, it is clear that FDA was not in any way addressing whether the agency *itself* needed a right of reference to access third-party documents, as Takeda suggests.

consult those studies and those data in that file in order to make its decision," the agency must not do so without taking further action). Surely the prior applicant's voluntary submission of its proprietary data to FDA waived any right that applicant may have had to prohibit FDA from "open[ing] th[e] locked file drawer" to access the applicant's data in the future. (*Id*. at 28:13.) And to extent that a drug sponsor's proprietary data contributes to the general body of scientific knowledge about what a particular pharmacological agent is or does, it is not at all clear that it would even be *feasible* to prevent FDA's scientists from applying that knowledge when other new drug applications are considered in the future. Moreover, and in any event, any agency effort to secure a "right of reference or use" from a prior applicant with respect to proprietary data such applicant previously submitted would almost certainly alert that prior applicant to the possibility of a potential new competitor, obviating any need for Hatch-Waxman's patent certification and notice process. Thus, Takeda's contention that FDA cannot consult or rely upon third-party data in the absence of a right of reference, or conversely, that it must secure such right if it desires to access third-party data, has practical implications that render the assertion manifestly inconsistent with the Hatch-Waxman scheme, which is perhaps why no such limitation on FDA authority is articulated anywhere in the FDCA or the agency's regulations—Takeda cites none, and as far as this Court can tell, the contention that "FDA had no right to use [proprietary third-party data] to approve a competing product" (Takeda Suppl. Mem. at 8; *see also id*. at 8-10) has been crafted entirely out of whole cloth.

Nor will it do for Takeda to insist that (fear not!) FDA actually *can* do what the law otherwise would not permit it to do when the agency undertakes to consider a

Section 505(b)(2) new drug application (*i.e.*, rely on third-party data without a right of reference), so long as the agency requires the applicant to certify to the patents that are related to the third party's drug product. (*See* Takeda Suppl. Mem. at 10 ("The statute expressly authorizes reliance on third-party data without a right of reference from the third-party. But the *quid pro quo* Congress established for using such data is that the 505(b)(2) application must identify the product for which the data was generated, as well as certify to any patents listed for that product."). In suggesting this simple solution to a problem of its own design, Takeda is merely igniting a straw man. That is, because there is no basis whatsoever for concluding that FDA's authority to rely on third-party data without a right of reference is limited, there is likewise no basis for Takeda's assertion that Congress has constructed a statutory scheme in which requiring patent certification is the "quid pro quo" for being relieved of that limitation.

Takeda also plainly struggles to reconcile its agency-reliance argument with what the agency has said repeatedly about when the patent certification obligation is triggered. For example, Takeda points to a Citizen Petition Response to Abbott Labs dated November 30, 2004, in which the agency stated that "[e]ach application will certify only to patents listed for drugs on whose finding of safety and effectiveness *FDA relies for approval* (including patents for pharmaceutical equivalents or, if there is no pharmaceutical equivalent, for the most similar alternative), not to patents submitted for applications on which FDA could have relied but did not." (Takeda Suppl. Mem. at 7 (emphasis in the original) (citing Ltr. from Steven K. Galson, Acting Dir., FDA Ctr. for Drug Evaluation and Research, FDA, to Donald O. Beers, Arnold & Porter LLP and William F. Cavanaugh, Jr., Patterson, Belknap, Webb & Tyler LLP at 10 (Nov. 30,

2004) (hereinafter "Fenofibrate Citizen Petition Response") (responding to Docket No. 2004P-0386/CP1 & RC1)).) But FDA made this statement in the context of a letter that rejects Abbott Labs's broad proposition that a Section 505(b)(2) applicant must certify "not only to the patents for the listed drug that [the] 505(b)(2) application references and on which it relies for approval, but also to all patents on all other later-approved [products in the same product line] that were approved based, in part, on some or all of the same underlying investigations[.]" (*Id*. at 1.) Read in context, FDA's use of the phrase "[e]ach application will certify only to patents listed for drugs on whose finding of safety and effectiveness *FDA relies for approval*" merely clarifies the limited scope of the applicant's patent certification obligation as far as the universe of drug products that may share the same underlying investigations are concerned, and it is by no means addressed to the question of whether the agency's own reliance on data outside that which is submitted or referred to in the 505(b)(2) application triggers the patent certification obligation.

Furthermore, in the course of pulling FDA's quotation out of context, Takeda has deftly sidestepped numerous instances in this same petition response in which FDA clearly explains that its policy regarding a Section 505(b)(2) applicant's patent certification obligations relates solely to *the applicant's* reliance, to wit:

> *[A] [S]ection 505(b)(2) applicant is permitted to rely* in whole or in part on the Agency's previous findings of safety and effectiveness for one or more previously approved drugs (listed drugs). As a condition of doing so, however, *the [S]ection 505(b)(2) applicant* must identify in its application the drug product or products *on which it relies* and certify to any relevant patents for those drug products. Patent certification obligations . . . are linked to identification of the listed drug or drugs *on which the application relies* and are limited to the patents submitted and published for the listed drug or drugs identified.

(*Id.* at 8 (emphasis added) (footnote omitted).) Thus, contrary to Takeda's argument, FDA makes clear in this Citizen Petition Response that the agency's own reliance on third-party data is not even *relevant* to a Section 505(b)(2) applicant's obligation to reference a drug and file a related patent certification, much less "the triggering event" for that obligation. (Takeda Suppl. Mem. at 6.)

In the final analysis then, this Court finds no basis for Takeda's contention that, as a matter of FDA policy, "[t]he ultimate reference and certification obligations depend on whether *FDA* relies on other studies or data." (Takeda Suppl. Mem. at 6 (emphasis in original).) Moreover, when Takeda makes the assertion that FDA's reliance on third-party data triggers the Section 505(b)(2) patent certification obligation under the Hatch-Waxman Act, it presents a puzzling conundrum: for all of Takeda's efforts to convince this Court that Congress intended for FDA itself to be a party to the Hatch-Waxman exchange—prohibited from consulting proprietary third-party data and information to approve a 505(b)(2) application unless it forces the applicant to certify to the owner's patents—it not only fails to identify any statutory or regulatory provision that says this, it also has failed to articulate any *benefit* that would redound to the agency (or the public) as a result of that supposed bargain. It is beyond dispute that Congress has entrusted FDA with the responsibility of making scientific determinations regarding the safety and effectiveness of marketed drug products—which, in and of itself, strongly indicates that Congress intended for the agency to have *more* data and information at its disposal, rather than *less*—and there can be no question that making science-based safety decisions is FDA's core function. Consequently, there is no reasonable explanation for the view that Congress somehow also intended for the

privilege that it has given FDA to access proprietary data and information in the fulfillment of its core responsibilities to be linked to, and potentially *hampered* by, a duty to protect third-party patent rights. (*See* MSJ Mot. Hr'g Tr. at 26:7-29:3.) Put another way, if Takeda is correct that, under the statutory scheme, "[t]he critical [patent certification] issue is whether third-party data were used [by FDA] to support the approval of a 505(b)(2) application" (Takeda Suppl. Mem. at 10), then another crucial question remains unanswered: *why* would Congress require the federal agency that is tasked with determining the safety and efficacy of new drugs to "lock" an agency file drawer that contains scientific data pertinent to the evaluation of a new drug marketing application (MSJ Mot. Hr'g Tr. at 28:13), and to access that information for the purpose of the agency's own review only if the agency first forces the applicant to certify to the data owner's patents?

b. Even If Agency Reliance On Third-Party Data Is Relevant, FDA Did Not Approve Mitigare In Reliance On Mutual's Information

Even if one were to accept Takeda's legal argument that *the agency's* reliance on third-party studies and data gives rise to an obligation on the part of the agency to require the applicant to reference the relied-upon drug product and certify to its patents, this Court concludes that the record here does not demonstrate FDA "reliance" on Colcrys in its approval of Mitigare in the relevant sense. Takeda tallies up the number of times that "Colcrys" appears in the administrative record—246—and, largely on this basis, asserts that FDA's approval of Mitigare was based, at least in part, on the Colcrys data. (*See* Takeda Suppl. Mem. at 5, 7; *see also* Takeda Reply Mem. at 18-22.) It is true that there are a substantial number of Colcrys mentions in the Mitigare record, and there are also tables and memos that indisputably demonstrate that FDA scientists

studied and compared the data that Mutual submitted with the data that West-Ward proffered. (*See id*. at 19-20; *see also, e.g.*, AR at 688, 692, 701.) But it is a big leap to conclude that "FDA plainly relied on Colcrys, over and over again" (Takeda Suppl. Mem. at 7) solely on this basis, nor is it necessarily the case that FDA's many mentions of the Coclrys studies were essential to FDA's findings that Mitigare is safe and effective as labeled. (*See* Takeda Reply Mem. at 21-22 (asserting that FDA "inherently relied" on Colcrys data).)

Takeda strongly suggests that every mention of—or reference to—Colcrys that the agency made during its consideration of the Mitigare application counts as an instance of "reliance" for the purpose of the patent certification obligation, and certainly that the combined *246 times* that the agency refers to Colcrys in the instant administrative record is sufficient to satisfy the reliance threshold for the purpose of the patent certification requirement. (*See, e.g.*, Takeda Suppl. Mem. at 3 ("[T]he agency repeatedly consulted and referred to Colcrys data in considering whether and how to approve Mitigare."); MSJ Mot. Hr'g Tr. at 6 (emphasizing "the number 246," as the number of Colcrys references in the record).) In this regard, however, Takeda is employing a "reliance" concept that is *much* broader than what Congress envisioned when it developed the Hatch-Waxman patent-certification scheme.

As will be discussed fully below in Part III.A.3, with the Hatch-Waxman Amendments to the FDCA, Congress established a drug approval system in which a Section 505(b)(2) applicant can satisfy the clinical research requirement by using the results of research studies that were not conducted by the applicant and "for which the applicant has not obtained a right of reference." 21 U.S.C. § 355(b)(1), (2). Here,

West-Ward conducted its own drug-drug interaction studies, and it also relied on published literature about colchicine and FDA's safety and efficacy findings for the drug Col-Probenecid. The fact that FDA considered the differences between what West-Ward's clinical studies found and what Mutual's clinical studies had concluded does not necessarily mean that West-Ward's own submissions had failed to show that Mitigare is safe and effective for the prophylaxis of gout independently of the Colcrys data. In fact, FDA specifically stated that, based on West-Ward's submissions alone, the agency had come to the conclusion that Mitigare is safe and should be approved. (*See, e.g.*, AR at 28-30 (Mitigare approval letter); *id*. at 162 (noting that "the clinical pharmacology data submitted by the applicant are sufficient for approval of this application for colchicine, and a product label can be written based on case reports described in the published literature and the specific clinical pharmacology studies conducted by the applicant"); *id*. at 170 ("No clinical pharmacology/biopharmaceutics deficiencies were identified in the original application for [Mitigare.]").) Thus, from the standpoint of the type of reliance that Section 505(b)(2) requires and that Congress clearly cares about, FDA did not "rely" on Mutual's Colcrys studies to fill in an identified gap in the safety and effectiveness studies that West-Ward submitted with its) application for Mitigare, as would ordinarily be the case when a Section 505(b)(2) applicant exercises its right of reliance on such studies under the statute.

Nevertheless, Takeda confidently maintains that sufficient reliance was achieved for the purpose of the Section 505(b)(2) patent certification obligations because FDA made repeated substantive references to Colcrys data during its review of the Mitigare application (Takeda Suppl. Mem. at 5)—in stark contrast to the scant number of times

that Col-Probenecid was referenced (MSJ Mot. Hr'g Tr. at 22:3-13)—and because "Mitigare's labeling . . . would make no sense if they hadn't looked at Colcrys' studies." (*Id*. at 62:10-12.) But, given the nature of the Section 505(b)(2) application process, Takeda's certitude that FDA's repeated references to the Colcrys data triggered the patent certification requirement seems unwarranted. In Takeda's world view, it might be the case that the type of reliance necessary to give rise to patent certification when an *agency* actively consults third-party studies and data can be different in nature from the applicant reliance that the Section 505(b)(2) process requires—*i.e.*, the fill-in-the gap variety—but Takeda has provided no basis upon which this Court can conclude that Congress intended any such distinction, and of course, that determination would be for Congress, not this Court, to make. In the meantime, even if this Court agreed with Takeda that a Section 505(b)(2) applicant's patent certification obligations are tied to the data that FDA consults when reviewing a Section 505(b)(2) application as a matter of law and FDA policy, Takeda has fallen short of making a persuasive argument that FDA's actions here—including its repeated "substantive references to Colcrys data" (Takeda Suppl. Mem. at 5)—qualify as the type of reliance that Congress intended to give rise to the patent certification obligation.[17]

[17] Even page 701 of the administrative record—which contains "FDA's assessment of the Colcrys data *when combined* with the Mitigare data" (Takeda Suppl. Mem. at 8 (emphasis added)), and which Takeda calls a "smoking gun" example of agency reliance (MSJ Mot. Hr'g Tr. at 12:25)—does not support the contention that FDA "relied" on the Colcrys data when it approved Mitigare in the sense that it was a basis for FDA's finding of safety and effectiveness. FDA was not expressing the agency's concerns or doubts about West-Ward's submissions regarding the safety of Mitigare, but instead was merely *comparing* the two different sets of data results that the two different colchicine products had generated about the potential interaction of 0.6 mg of colchicine with the same two classifications of drugs. Indeed, FDA's "telling" statement (Takeda Suppl. Mem. at 8) does not appear to be about the safety of Mitigare or Colcrys at all, but is a statement about *the nature of P-gp and CYP3A inhibitors*, in light of what, combined, the Colcrys and Mitigare data showed. (*See* AR 701 (concluding that "West-Ward and Mutual's DDI data combined, suggests that P-gp inhibition may play a more dominant role than CYP3A4 inhibition").)

2. Under FDA's Procedural Rules, An Applicant—Not FDA—Has The Right To Choose The "Most Appropriate" Or "Most Similar" Reference Drug For Its 505(b)(2) Application

The second "procedural requirement" that Takeda and Elliott argue FDA violated when it approved Mitigare without requiring a reference to Colcrys and certifications to the Colcrys patents has to do with the drug that a Section 505(b)(2) applicant selects as its reference listed drug. (*See* Takeda Suppl. Mem. at 13-18.) Takeda cites a Citizen Petition Response in which FDA states that a "505(b)(2) applicant should determine which listed drug(s) is *most appropriate* for its development program[,]" (*id*. at 13-14 (citing Ltr. from Janet Woodcock, Dir., Ctr. for Drug Evaluation & Research, FDA, to David B. Clissold, Hyman, Phelps & McNamara, P.C., at 8 (Sept. 18, 2013) (hereinafter "Suboxone Citizen Petition Response") (responding to Citizen Petition Dkt Nos. FDA-2011-P-0869 & FDA-2013-P-0995) (emphasis added))), and it argues that, because of the similarities between Colcrys and Mitigare, Colcrys, rather than Col-Probenecid, was the "most appropriate" listed drug for Mitigare to reference. (*See* Takeda Suppl. Mem. at 13-18.) Elliott joins in this contention, putting a slightly different spin on the argument (*see* Elliott MSJ Mem. at 41-42); ultimately, though, both Plaintiffs insist that West-Ward was required to identify Colcrys as the reference listed drug for its proposed new drug Mitigare "[u]nder FDA's governing standard," such that FDA acted arbitrarily and capriciously in failing to insist that West-Ward follow this rule. (Takeda Suppl. Mem. at 13; *see* Elliott MSJ Mem. at 41 (arguing that FDA has a policy of requiring applicants to reference and certify to "the most similar drug with the most current safety and efficacy data").)

Both Plaintiffs are mistaken. Put bluntly, their argument hinges on the existence of an FDA drug reference policy that does not exist. First, the Citizen Petition

Response that Takeda says shows that an applicant must select the reference drug that is "most appropriate" contains the clear disclaimer that "this suggested approach does not reflect a statutory or regulatory requirement." (Suboxone Citizen Petition Response at 7). Then, when one actually reads that document, FDA clearly states that "*a sponsor* interested in submitting a 505(b)(2) application that relies upon FDA's finding of safety and/or effectiveness for one or more listed drugs *should determine which listed drug is most appropriate for its development program*." (*Id*. (emphasis added).). FDA also provides a clear explanation as to why the agency has chosen to cede the reference determination to the applicant in this way: because, under the Section 505(b)(2) scheme, the applicant uses the reference listed drug to supply safety and effectiveness data in total or partial fulfillment of the applicant's obligation to prove that its drug is safe and effective—meaning that there is a direct correlation between the drug the applicant chooses to reference and the applicant's burden of proof. (*See id*. ("An applicant choosing to rely on FDA's finding of safety and/or effectiveness for a listed drug very similar to the proposed product submitted in the 505(b)(2) application would generally need to submit less additional data to support the differences between the proposed product and the listed drug for approval of the 505(b)(2) application.").) Thus, it is FDA policy that, "so long as a sponsor provides the necessary data and information to support the difference(s) between the reference drug and its proposed drug, and so long as the proposed drug is not an exact duplicate of the reference drug, a sponsor is free to choose the listed drug that *it* deems 'most appropriate' for reliance in its 505(b)(2) application." (FDA Suppl. Mem. at 3; *see also* Fenofibrate Citizen Petition Response at 9 ("[B]ecause, under 21 CFR 3 14.54(a), a 505(b)(2) applicant

seeking approval for a change to a listed drug need only supply information sufficient to support the change proposed, it follows that the more similar a proposed drug is to the listed drug cited, the smaller the quantity of data that will be needed to support the proposed change.").)

To be sure, in the Suboxone Citizen Petition Response, FDA states that "the applicant should identify the pharmaceutically equivalent product as a listed drug relied upon[,]" and "should determine which listed drug(s) is most appropriate for its development program." (Suboxone Citizen Petition Response at 7; *see also* Takeda Reply Mem. at 17-19.) But the agency also warns that "the determination of which listed drug is 'most similar' to a proposed product may be difficult (except in cases in which a pharmaceutical equivalent previously has been approved)[,]" and that this reference determination is "dependent on the sponsor's approach to its development program." (Suboxone Citizen Petition Response at 7.) When all of the agency's statements are read in context, then, it is clear that FDA's policy is to view the "most appropriate" drug to be whatever drug fills in the gaps in the data the drug sponsor submits to support the sponsor's contention that the drug is safe and effective, and *not* whatever listed drug is most similar in nature to the one the applicant proffers, as Takeda and Elliott maintain.[18]

Elliott's attempt to craft a mandatory reference policy out of the agency's supposed "most similar drug" requirement fares no better. (Elliott MSJ Mem. at 38-42

[18] This is not to suggest that FDA relinquishes to the applicant the *ultimate* determination of whether or not the referenced drug studies successfully fill the research gap in an applicant's portfolio. FDA makes *that* determination, and it may certainly reject a Section 505(b)(2) application if, in the agency's own expert judgment, the investigations and studies that the applicant refers to do not demonstrate that the applicant's drug is safe and effective. What the agency does *not* do is what Plaintiffs here suggest: it does not to force a Section 505(b)(2) applicant to reference the drug product that is most pharmacologically similar to the applicant's own product.

(citing Fenofibrate Citizen Petition Response).) In essence, Elliott argues that FDA has a long-standing policy of "prohibiting 505(b)(2) applicants from circumventing the FDCA's patent certification requirements" (*id.* at 38), and that the requirement that an applicant reference the "most similar drug" in its Section 505(b)(2) application (Fenofibrate Citizen Petition Response at 9) does the work of enforcing this objective insofar as it constrains sponsors who select the 505(b)(2) pathway as a means of "shirk[ing]" their patent certification obligations. (Elliott MSJ Mem. at 38.) But Elliott provides no evidence that FDA actually monitors or mandates a "most similar drug" requirement *within the 505(b)(2) context* (*see id*. at 38-39 (providing only examples of ANDAs)), much less that the agency views this alleged requirement as a mechanism for keeping applicants who approach the agency with a questionable Section 505(b)(2) application in line. Nor has Elliott explained how any supposed FDA policy of restraining a Section 505(b)(2) applicant's discretion regarding the reference drug jibes with the agency's well-established reasons for permitting the applicant itself to make the reference determination. (*See* FDA Suppl. Mem. at 2-3; FDA XMSJ Mem. at 15-16.)[19]

This Court also notes that, in addition to the lack of any policy on the part of FDA regarding which drug must be referenced in a Section 505(b)(2) new drug application, there is also no record evidence that clearly demonstrates that the mere

[19] This is, of course, is precisely why this Court cannot accept Elliott's argument that FDA diverged from its own policies in an arbitrary and capricious fashion when it refused to insist that West-Ward—a Section 505(b)(2) applicant—follow the same reference and certification procedures as an ANDA applicant must follow. (*See* Elliott MSJ Memo at 38-42.) FDA's alleged "long-standing anti-circumvention policy" (*id.* at 39) is not in conflict with its equally long-standing view that the ANDA and Section 505(b)(2) pathways differ substantially. To assert that FDA somehow violated the former because it evaluated Mitigare as a Section 505(b)(2) application does not establish any APA violation; rather, it merely begs the question of whether, under FDA's rules, the agency properly permitted West-Ward to proceed as a 505(b)(2) applicant in the first place.

existence of "similar" approved drug products matters to FDA in practice. Takeda seems to think it does—one of its briefs takes care to explain Colcrys's own reliance on Col-Probenecid— a dissimilar combination drug product—by emphasizing that, "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[,]" and adding: "[t]hat was no longer true by the time [West-Ward] submitted its Mitigare application." (Takeda Reply Mem. at 18 n.6.) But Takeda does not, and apparently cannot, show that the general state of the market at the time that a Section 505(b)(2) application is submitted is relevant to FDA's assessment of whether a Section 505(b)(2) applicant has established the safety and effectiveness of its new drug product. And without such proof, Plaintiffs are hard-pressed to demonstrate that the agency has a policy of requiring an applicant to reference the listed drug product that is "most similar" to the applicant's own.

The bottom line is this: FDA's prior statements confirm that, other than where duplicate drug products are involved, a Section 505(b)(2) applicant has the discretion to select a reference drug, and to make that selection in relation to the scope of the materials the applicant desires to submit. (*See* Fenofibrate Citizen Petition Response at 8-10; Suboxone Citizen Petition Response at 8-10; AR at 12-14 (Colchicine Citizen Petition Response).) Thus, to the extent that the agency has any "policy" about what drug should be referenced in a Section 505(b)(2) application, FDA has decided to leave it up to the drug sponsor to determine whether the sponsor would like to do less work and rely on a very similar drug, or do more work and rely on a dissimilar drug. (*See id*.) Given that policy choice—which is the opposite of Elliott's ANDA-related

assertion that "[u]nder longstanding FDA policy, applicants do not have unfettered discretion to choose any prior drug as the reference listed drug" (Elliott MSJ Mem. at 41)—neither the agency nor West-Ward needs to provide any explanation as to "why Col-Probenecid was more similar or more appropriate for [West-Ward] to cite than Colcrys" (Takeda Reply Mem. at 17). Regardless, it is clear that Plaintiffs' argument that FDA violated its own procedural rules when it refused to force West-Ward to reference the obviously most similar/appropriate drug (Colcrys) fails.

3. The FDCA Unambiguously Requires A Section 505(b)(2) Applicant To Certify Only To Patents Associated With The Reference Listed Drug

Whereas Takeda's patent certification argument is primarily about whether, and to what the extent, FDA's approval process for Mitigare relied on Colcrys data, Elliott maintains that FDA should have required West-Ward to certify to the Colcrys patents regardless. Elliott's contention is primarily a statutory one: that the text of the FDCA required West-Ward to file a certification to the Colcrys method-of-use patents when it sought FDA approval for Mitigare, even if West-Ward did not rely on the investigations or data underlying Colcrys in its application for approval. (*See* Elliott MSJ Mem. at 23-28.) In this regard, Elliott homes in on language in subdivision (A) of 21 U.S.C. § 355(b)(2); specifically, the statement that a Section 505(b)(2) application must include "a certification . . . with respect to each patent which claims the drug for which such investigations were conducted *or which claims a use for such drug for which the applicant is seeking approval under this subsection*[.]" 21 U.S.C. § 355(b)(2)(A) (emphasis added).[20] As Elliott reads this statute, Congress intended Section 505(b)(2)

[20] The full text of Section 505(b)(2)(A) states that:

applicants to certify not only to the product and method-of-use patents that claim the drug product upon whose investigations the applicant relied in seeking approval for the new drug—*i.e.*, every patent for the reference listed drug—but also to certify to all "controlling use patents" related to the underlying drug substance, even if the product associated with the use patent is not the drug product referenced in the Section 505(b)(2) application—*i.e.*, all patents "'claim[ing] a use for such drug for which the applicant is seeking approval[.]'" (Elliott MSJ Mem. at 25 (quoting 21 U.S.C. § 355(b)(2)(A)); *see also id.* (explaining that the second requirement is focused "on the uses for the drug for which the applicant is seeking approval, not the investigations upon which the applicant relies").) Because there are four Colcrys patents listed in the Orange Book claiming a method of using colchicine for the prophylaxis of gout, Elliott argues that the FDCA required West-Ward to include in its application for approval of Mitigare certifications to the Colcrys patents, and the fact that West-Ward did not make any such certifications means that FDA's approval of Mitigare "was in excess of its statutory authority and must be vacated under the APA." (*Id.* at 23.)

> (2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include--
>
> (A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section--
>
> (i) that such patent information has not been filed,
> (ii) that such patent has expired,
> (iii) of the date on which such patent will expire, or
> (iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted[.]

21 U.S.C. § 355(b)(2)(A).

As a threshold matter, Elliott is correct that the APA requires a reviewing court to set aside FDA's final action in approving a drug product for marketing if the court finds that that approval violates limitations that a federal statute imposes. *See* 5 U.S.C. § 706 (2)(C); *see, e.g.*, *Am. Bioscience, Inc. v. Thompson*, 269 F.3d 1077 (D.C. Cir. 2001) (holding that FDA improperly approved an ANDA for a generic form of a patented drug because FDA had arbitrarily and capriciously removed a new patent from the Orange Book listing and approved the ANDA without requiring the competitor to address the de-listed patent); *Bayer HealthCare, LLC v. FDA*, 942 F. Supp. 2d 17 (D.D.C. 2013) (suspending FDA's approval of an ANDA where FDA had approved the application for a generic version of plaintiff patent owner's drug without responding to plaintiff's Citizen Petition for years and without providing a reasoned basis for rejecting the petition). Courts review FDA's own interpretation of what the FDCA (the agency's organic statute) permits under the two-step framework of *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984), *see, e.g.*, *AstraZeneca Pharm. LP v. FDA*, 713 F.3d 1134, 1139 (D.C. Cir. 2013); *Apotex, Inc. v. FDA*, 226 Fed. Appx. 4, 5 (D.C. Cir. 2007); *Teva Pharm. Indus. Ltd. v. Crawford*, 410 F.3d 51, 53 (D.C. Cir. 2005)—a staged analysis that requires the court to consider, first, "whether Congress has spoken to the precise question at issue. If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Chevron*, 467 U.S. at 842-43. If there is no clear answer, however, the court must proceed to the second step, which involves giving deference to FDA's interpretation of the statute so long as FDA's reading of the statute is "based on a permissible construction." *Id.* at 843.

The statutory question that Elliott raises here is, in essence, whether 21 U.S.C. § 355(b)(2)(A) requires not only certification to those patents that claim the drug *product* on whose investigations the 505(b)(2) applicant relied (*i.e.*, the reference listed drug), but also certification to all patents that claim a method of using the drug *substance* (*i.e.*, the active ingredient) in the new drug product that the applicant has proffered for approval. To determine whether Congress has spoken directly this issue under the first step of the *Chevron* analysis, this Court must use the traditional tools of statutory construction, which include an examination of the statute's text, structure, purpose, and legislative history. *See*, *e.g.*, *Stat-Trade Inc. v. FDA*, 869 F. Supp. 2d 95, 102 (D.D.C. 2012); *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1319 (D.C. Cir. 1998)); *Eagle Broad. Grp., Ltd. v. FCC*, 563 F.3d 543, 552 (D.C. Cir. 2009). Notably, after wielding these standard implements in the context of this case, the parties here not only have competing interpretations of subsection (b)(2)(A)'s plain text, they also differ as to whether this statutory subsection is ambiguous.[21] However, this Court finds that Congress' intent regarding the scope of a Section 505(b)(2) applicant's patent certification obligation is clear on the face of the statute: such applicant need only certify to the product patents or the method-of-use patents that are associated with the reference listed drug (*i.e.*, the drug product on whose investigations the 505(b)(2) applicant relies).

[21] Elliott argues that Congress unambiguously intended to protect all method-of-use patent holders regardless of whether a Section 505(b)(2) applicant references that patent holder's drug, and thus that the Court's evaluation of § 355(b)(2)(A) should stop at *Chevron* Step One. (*See* Elliott MSJ Mem. at 23.) West-Ward also argues that the Court's analysis should stop at *Chevron* Step One, but unlike Elliott, West-Ward insists that Hatch-Waxman unambiguously requires a Section 505(b)(2) applicant to certify only to patents associated with the listed drug on which the applicant relies for approval. (*See* West-Ward XMSJ Mem. at 7-16.) For its part, FDA argues that the statute could be interpreted either way—*i.e.*, it is ambiguous—but the agency's interpretation is reasonable and is therefore entitled to deference at *Chevron* Step Two. (*See* FDA XMSJ Mem. at 7-13.)

Examining the text of the statute, one must begin at the beginning, recognizing that the language of section 355 of Title 21 opens with an unmistakably clear mandate to sponsors of new drugs: before any new drug can be marketed, the sponsor must seek FDA approval for the drug by filing an application with FDA that includes certain specified components. *See* 21 U.S.C. § 355(a) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug."). Subsection (b)(1), which clarifies that "[a]ny person may file with the [agency] an application with respect to any drug[,]" states that, "as a part of the application[,]" the applicant "shall submit" to the agency several pieces of information, including:

> *(A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use*; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title.

21 U.S.C. § 355(b)(1) (emphasis added).

The dispute at issue here involves new drug applications that seek to satisfy the clause (A) "investigations" requirement by relying on studies that "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted[.]" *Id.* § 355(b)(2). Congress specifically addresses this circumstance in subsection (b)(2).

Pursuant to that subsection, when an applicant wishes to rely on the safety and efficacy investigations that were conducted with respect to another drug and the applicant has not secured the right to reference those studies, additional application materials must be submitted. Specifically, the statute requires the applicant to make certain patent-related representations: "(A) a certification . . . with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval[,]" *id.* § 355(b)(2)(A), and also, if applicable, (B) "a statement" that confirms that an existing method-of-use patent "with respect to the drug for which investigations . . . were conducted" "does not claim a use for which the applicant is seeking approval under this subsection," *id.* § 355(b)(2)(B). In this Court's view, the plain text of subdivision (b)(2) unambiguously evidences Congress' intent to require a patent certification to be filed only with respect to patents that either claim the drug product that is the basis for the investigations upon which the applicant is relying (the reference listed drug), or that claim a method of using the reference listed drug for which the applicant is seeking approval.

The textual support for this conclusion is abundant. First, Congress lists the patents for which certifications are required *in a single sentence*—without break or numerical delineation—indicating that the categories of patents being referred to in this single run-on statement are generally of the same type and bear some relationship to one another, *i.e.*, both relate to the reference-listed drug, as opposed to being of an entirely different species. *See DeNaples v. Office of Comptroller of Currency*, 706 F.3d 481, 490 (D.C. Cir. 2013). Second, the disputed clause uses the word "drug" twice when identifying the patents that require certification: every patent "which claims the

drug for which such investigations were conducted or which claims a use for such *drug* for which the applicant is seeking approval under this subsection[.]" 21 U.S.C. § 355(b)(2)(A). Although the term "drug," as used in the FDCA, can refer to both the finished drug product and also its active ingredient, *see* 21 U.S.C. § 321(g)(1), the fact that Congress repeated the word "drug" twice within such a short span of text strongly suggests that it intended the *same* definition to apply to that term. *See Brown v. Gardner*, 513 U.S. 115, 118 (1994) (explaining that the presumption that a given term is used to mean the same thing throughout a statute is "surely at its most vigorous when a term is repeated within a given sentence"). Thus, construing "drug" to mean the referenced and relied-upon drug product in both places in the disputed clause of section (b)(2)(A) is manifestly superior to Elliott's interpretation of the text, which requires that same word to be given two different meanings within the same sentence. (*See* Elliott MSJ Mem. at 25-27 (arguing that the drug "for which the applicant is seeking approval" refers to the drug *substance* (colchicine), whereas the "drug for which such investigations were conducted" refers to the referenced drug *product* (here, Col-Probenecid)).

The fact that Congress uses the phrase "*such* drug" after the conjunction further indicates its intent to reference only *one* drug—the drug for which the relied-upon investigations were conducted—in section (b)(2)(A). The term "such," when used as an adjective, is an inclusive term, showing that the word it modifies is part of a larger group. *See, e.g.*, *Black's Law Dictionary* 1446 (7th ed. 1999) (defining "such" as "[o]f this or that kind," or "[t]hat or those; having just been mentioned"); *Am. Heritage Dictionary of the English Language* 1285 (New College ed. 1976) (defining "such" as

"[b]eing the same as that which has been last mentioned or implied"). Relatedly, and even more important, "such" nearly always operates as a reference back to something previously discussed. *See United States v. Ashurov*, 726 F.3d 395, 398-99 (3d Cir. 2013) (citation, internal quotation marks, and alterations omitted) (noting that it is "a commonly recognized rule in American jurisprudence that the word 'such' naturally, by grammatical usage, refers to the last precedent"); *United States v. Chi Tong Kuok*, 671 F.3d 931, 945 n.8 (9th Cir. 2012) ("'Such' in this context means 'of the sort or degree previously indicated or implied.'") (quoting Webster's Third New Int'l Dictionary 2283 (2002); *Nieves v. United States*, 160 F.2d 11, 12 (D.C. Cir. 1947) ("The word 'such' is restrictive in its effect and obviously relates to an antecedent.").

Thus, in accordance with its plain meaning, the term "such drug" unambiguously refers back to the "the drug for which such investigations were conducted"; much like "such investigations" plainly refers back to "the investigations . . . relied upon by the applicant for approval of the application[.]" 21 U.S.C. § 355(b)(2)(A). By contrast, Elliott's reading of subsection (b)(2)(A) ignores "such" entirely, and essentially replaces it with "the," so that the statute requires an applicant to submit a certification "with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for [~~such~~ *the*] drug for which the applicant is seeking approval." As much as Elliott may wish that Congress had employed another article in the method-of-use clause of subsection (b)(2)(A), Congress selected "such," and this Court is required to take Congress at its word. *See Am. Meat Inst. v. USDA*, 968 F. Supp. 2d 38, 56 (D.D.C. 2013) ("Plaintiffs . . . cannot escape the fact that the North

Star of any exercise of statutory interpretation is the intent of Congress, as expressed in the words it uses.").

Turning to an examination of the overall structure of the statute, this Court finds that its view of the plain meaning of § 355(b)(2)(A) is only reinforced. This is because the certification subsection is clearly embedded in a section of the statute that mandates reliance upon another drug's investigations as a non-negotiable prerequisite to any additional action on the part of the applicant. *See* 21 U.S.C. § 355(b)(2). The fact that the entire Section 505(b)(2) process concerns applications that rely, at least in part, on the safety and effectiveness finds of another drug, lends clear credence to FDA's argument that reliance matters under this statutory scheme (*see* FDA XMSJ Mem. at 11-13), and it certainly casts doubt on Elliott's assertion that the drug the Section 505(b)(2) applicant references and relies upon is essentially irrelevant to an applicant's obligation to certify to patents that may be infringed by the proffered product's method of use.

Adding to the structural difficulty with Elliott's proposition is the fact that the subsection (b)(2)(A) certification requirement—which, according to Elliott, Congress intended to be completely unmoored from the essential reliance underpinnings of the Section 505(b)(2) process—is followed by a subsection that concerns itself expressly with the method-of-use patents "with respect to the drug for which investigations . . . were conducted." 21 U.S.C. § 355(b)(2)(B). This subsection requires an applicant to file a "statement" in lieu of a certification, when the method-of-use patents for the referenced and relied-upon drug cover uses that are not the same as the uses for which the applicant seeks approval. (*Id.*) Thus, as FDA explains, this subsection clearly

works in conjunction with subsection (b)(2)(A), to address all method-of-use patents for the reference listed drug, whether or not the 505(b)(2) applicant is seeking approval for a patented use.[22] Elliott's alternative reading would mean that, in subsection (b)(2)(A), Congress intended for applicants to certify to all of the method-of-use patents that exist related to uses of the active ingredient in the applicant's drug, but somehow the disclaimer of potentially infringing use (in subsection (b)(2)(B)) is only required with respect to the method-of-use patents related to the reference listed drug. Elliott provides no reason for why Congress would do such a thing, and this Court sees none.

It is also clear that the fundamental purpose of the Hatch-Waxman Amendments themselves confirms this Court's reading of subsection (b)(2)(A). As has been stated repeatedly above, Congress intentionally designed Hatch-Waxman to balance two important and potentially conflicting objectives: incentivizing investment in the innovation of new drugs, and encouraging the production of less-costly alternative drug products. *Janssen Pharmaceutica, N.V.*, 540 F.3d at 1355. To ensure that *both* of these goals are achieved, Congress constructed a system in which having to certify to patents and provide the patent owners with notice (protecting the innovator's work product) is the price that a new drug applicant pays for being able to rely on work already approved (promoting efficient drug development). *See* 21 U.S.C. § 355(b)(2). (*See also* Fenofibrate Citizen Petition Response, at 11 ("To divorce patent certification

[22] FDA provides an illuminating example: "Although neither of the patent certification requirements from Section 505(b)(2)(A) apply here because no patents are listed for Col-Probenecid (the listed drug upon which West-Ward relied), if, hypothetically, there were two method-of-use patents listed for Col-Probenecid, one concerning prophylaxis of gout flares and one concerning treatment of acute gout flares, and West-Ward were seeking approval of Mitigare only for prophylaxis of gout flares, then West-Ward would only have to file a certification to the patent concerning that use (i.e., the use of Col-Probenecid 'for which the applicant is seeking approval')." (FDA XMSJ Mem. at 12.) "In that hypothetical situation, West-Ward would also have had to file a statement pursuant to [S]ection 505(b)(2)(B) explaining that the use patent listed for Col-Probenecid for treatment of acute gout flares does not claim a use for which the applicant is seeking approval." (*Id*. at 12 n.7.)

obligations from reliance and require [an applicant] to certify to patents on additional drug products on which FDA did not rely for approval would upset the delicate balance struck by the Hatch-Waxman Amendments.").) This *quid pro quo* arrangement is preserved if subsection (b)(2)(A) is interpreted as it was written—to require a new drug applicant to certify to the product and method-of-use patents that are related to the drug the applicant references and relies upon for approval—and is effectively undone if, as Elliott insists, the applicant's certification obligation does not depend at all on the applicant's reliance on another's work product, and instead applies across-the-board, to any and all patented drugs that share the same active ingredient and thus have a potential to be infringed (however remote that potential may be). As FDA points out, "there is no *quid pro quo* in the scenario that Elliot proposes; there is only a benefit for patent owners whose data is not being relied on by another manufacturer." (FDA XMSJ Mem. at 10.) And from the standpoint of what Congress intended, if Congress really meant to tip the carefully-balanced Hatch-Waxman scales so dramatically toward the protection of innovator's patent rights, there would be no reason for the statute to so clearly reflect Congress's interest in achieving that balance at all.[23]

[23] The House Committee on Energy and Commerce's statement that "the applicant must certify" with respect to "all product patents which claim the listed drug and all use patents which claim an indication for the drug for which the applicant is seeking approval," H.R. Rep. No. 98-857, pt. 1 at 32, does little to bolster Elliott's contention that Congress' primary interest in crafting the Hatch-Waxman *quid pro quo* scheme was the protection of *all* innovator's patent rights as far as method-of-use patents are concerned, without regard to an applicant's reliance on the innovator's studies. (See Elliott MSJ at 28-31.) As this Court reads it, this sentence from the House Report says no more than what the statute states: that, where an applicant seeks approval for a use of his drug that is the same as one claimed by the listed drug the applicant references and relies upon, then the applicant must certify to the referenced drug's method-of-use patents. Indeed, in the very same paragraph from which Elliott draws the quotation, the Committee suggests that it intends for the statute to be read in precisely this fashion. *See* H.R. Rep. No. 98-857, pt. 1 at 32 (explaining that a 505(b)(2) NDA "must include a certification by the applicant regarding *the status of certain patents applicable to the listed drug* if such information has been provided to the FDA" (emphasis added)); *see also id.* at 33 (hypothesizing a referenced drug that is "approved for two indications" and explaining that "[i]f the applicant is seeking approval for indication No. 1, and not indication No. 2 because it is protected by a use patent, then the applicant

For all these reasons, this Court is convinced that subsection (b)(2)(A) must be read in accordance with the plain meaning of its terms, and that those terms unambiguously describe two related types of patents that require certification when an applicant files a Section 505(b)(2) application in reliance on another drug's safety and efficacy studies: patents that claim the reference listed drug and patents that claim a method of using the reference listed drug, so long as the applicant is seeking approval for that patented use. In this regard, the phrase "for which the applicant is seeking approval" plainly relates to the term "use"—as in, "which claims a *use* for such drug *for which the applicant is seeking approval*"—and not, as Elliott argues, the term "drug"—as in "which claims a use for such *drug for which the applicant is seeking approval*" (*see* Elliott MSJ Mem. at 26-28). As a practical matter, this means that the statute requires certification for any product patents for the reference listed drug and/or any patents that claim a use for that same drug, if the applicant is seeking approval for that use. This reading does not render the statute redundant, or the method-of-use clause superfluous, because product patents and method-of-use patents are two different things, and one or the other patent type (or both) can apply to the referenced listed drug product; for example, when a product patent for the reference listed drug does not exist or has expired but there is nevertheless a valid and enforceable patent for a method of *using* that drug product. *See Caraco Pharm. Labs., Ltd.*, 132 S. Ct. at 1676 ("[P]atents come in different varieties. One type protects the drug compound itself. Another kind—the one at issue here—gives the brand manufacturer exclusive rights over a particular method of using the drug. In some circumstances, a brand manufacturer may

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must make the appropriate certifications and a statement explaining that it is not seeking approval for indication No. 2").

hold such a method-of-use patent even after its patent on the drug compound has expired.").[24]

In short, Elliott has cast aside all of the very clear textual indications that Congress intended a Section 505(b)(2) applicant to certify only to the patents that are associated with the drug that the applicant referenced and relied upon and, nevertheless, insists that, where method-of-use patents are concerned, Congress meant to jettison the reference listed drug product entirely and to require certification with respect to all patents that claim a use for the active ingredient that is in the applicant's new drug. This Court has little doubt that Elliott's reading is a distortion of the statutory text, rather than a statement of its unambiguous plain meaning. But even if there were any ambiguity in statute, and it thus became necessary to proceed to the second step of the *Chevron* analysis, this Court believes that it is entirely reasonable for FDA to interpret the certification provision in subsection (b)(2)(A) to require a Section 505(b)(2) applicant to certify only to the product and use patents that claim the reference listed drug, which, according to FDA, has been its long-held view of the statute. (*See* FDA XMSJ Mem. at 11.)[25] The instant administrative record establishes that FDA's position

[24] One need look no further than Colcrys itself to find a suitable example. Apparently, Mutual was not able to secure a product patent for Colcrys, given that Mutual did not create or develop colchicine, which has been used as a drug for the treatment of gout for centuries. (*See* AR at 3.) What Mutual *was* able to patent, however, is its research and findings related to the dosages of colchicine to be used in certain instances for the prophylaxis of gout and the treatment of acute gout flares; as noted, according to Elliott, there are at least four such "method of use" patents for Colcrys in FDA's Orange Book. (*See* Elliott MSJ Mem. at 17; *see also* AR at 8 (listing the patents for Colcrys in the Orange Book at the time of FDA's 2011 Colchicine Citizen Petition Response).) Presumably, if a future Section 505(b)(2) applicant relies on Colcrys to support its application for a new drug for the prophylaxis of gout or the treatment of gout flares, that Section 505(b)(2) application would need to reference Colcrys and to certify to any patent that "claims a use" for Colcrys, notwithstanding the fact that no Colcrys product patents exist.

[25] This means Elliott is mistaken once again when it contends, as a corollary to its statutory argument, that "longstanding FDA policy makes clear that patents claiming the indication for which approval is sought must be addressed through the certification process." (Elliott MSJ Mem. at 42.) To support this assertion, Elliott points to—and misconstrues—21 C.F.R. § 314.50(i)(1)(iii)(B), which concerns proper

is that "[t]he language of [S]ection 505(b)(2) of the Act explicitly links the *drug* relied on for approval to the *drug* for which patent certifications must be made. . . . FDA interprets *drug* in [S]ection 505(b)(2) to refer to *drug product*, not *active ingredient*[,]" Fenofibrate Citizen Petition Response at 6-7 (emphasis in original), and this Court's view of the reasonableness of this interpretation is inherent in its findings regarding Congress's intent with respect to that statute, which have been explained at length above. Suffice it to say here that "[t]here is nothing plainly wrong or impermissible about this statutory interpretation; indeed, based on the analysis above, the agency's view of the statute . . . is entirely reasonable." *Am. Meat Inst.*, 968 F. Supp. 2d at 59. Thus, even if a *Chevron* Step Two analysis was warranted, deference to FDA's reasonable interpretation of the statute would be warranted as well, and Elliott's statutory argument would fail.

B. FDA's Approval Of Mitigare Was Not An Unreasoned Change Of The Agency's Prior Position Regarding Single-Ingredient Oral Colchicine Products

Shifting away from the patent certification issue that is at the heart of the instant action, Takeda also trains its focus on the extent to which FDA has permitted Mitigare's label to differ from Colcrys. The basis for this attack on FDA's approval of Mitigare is

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labeling and makes only the unremarkable statement that, if the labeling of the "drug product for which the applicant is seeking approval includes *an indication that . . . is claimed by a use patent*, the applicant shall submit an *applicable* certification." *Id.* (emphasis added). Elliott reads this regulation to mean that it is FDA's policy that *all* method-of-use patents claiming the same indication as the applicant's drug must be certified to, but that is not what the regulation says; indeed, consistent with the FDCA, FDA has long maintained that the only "applicable" patent certifications are those that are made in relation to product or use patents that claim the reference listed drug. In its zeal to underscore the argument that the FDA's statement in the regulation contravenes the agency's present representations of its own policy, Elliott also fails to appreciate that the regulation it points to is part of set of agency rules that use nearly identical language to that of Section 505(b)(2)(A) of the FDCA. *Compare* 21 C.F.R. § 314.50(i)(1)(i) *with* 21 U.S.C. § 355(b)(2)(A). Thus, ultimately, Elliott has made the entirely circular argument that language in an FDA regulation that is nearly identical to the disputed statutory provision says what Elliott thinks the statute says.

the fact that the agency previously and specifically addressed the labeling of single-ingredient oral colchicine products in a response to a Citizen Petition that Mutual filed in 2010. (*See* AR at 18-20, 24.) As explained above (*see supra* Part I.D.1), when Mutual learned that West-Ward had submitted an application for a single-ingredient oral colchicine product that was identical to Colcrys, Mutual filed a petition that asked that the agency to restrict the marketing of such products in the future, by, among other things: (1) "[r]equir[ing] labeling for any single-ingredient oral colchicine product to include all information related to drug-drug interactions that is in the Colcrys labeling including relevant dose adjustments needed to prevent unnecessary toxicity; " (AR at 1), and (2) "not allow[ing] an applicant to carve-out the protected gout flares labeling information because the information is essential to prophylaxis." (*Id*. at 22.) Takeda now reads FDA's written response to this request, which the agency filed in 2011, as establishing "two specific labeling requirements" that Takeda says the agency arbitrarily and capriciously "abandoned" three years later with the approval of Mitigare: "one pertaining to the low-dose regimen for treating gout flares that occur during prophylaxis, and one pertaining to specific safety data showing drug-drug interactions." (Takeda Suppl. Mem. at 18.) As this Court reads the record, however, FDA did no such thing.

To begin with, it cannot reasonably be asserted that FDA's Colchicine Citizen Petition Response established an agency policy that the labels for single-ingredient oral colchicine products *must* contain *all* of the drug-drug interaction information that appears on the Colcrys label, as Takeda maintains. To support this position, Takeda interprets a sentence from the 27-page Citizen Petition Response—the statement 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" (AR at 3)—to mean that the labels of all future single-ingredient oral colchicine products have to contain the specific results of Mutual's drug-drug interaction studies, including Colcrys's dose-modification tables. (*See* Takeda Reply Mem. at 10-11, 15; *see also, supra*, Part I.C.3.) However, FDA's carefully worded statement does not go nearly that far; rather, the agency agrees only that the labeling of such products must contain "*adequate* information on drug-drug interactions, including *relevant* dose adjustments needed to prevent unnecessary toxicity." (AR at 19-20) (emphasis added).)

Accordingly, when it came time for FDA to evaluate the proposed label for Mitigare, and, in particular, to make a determination regarding what dose instructions would adequately inform patients taking Pg-p and CYP3A4 inhibitors how to use the product safely for prophylaxis of gout, FDA engaged in an extensive analysis of this very issue. Among other things, the agency looked at the drug-drug interaction instructions on the Colcrys label and the studies Mutual had conducted regarding the interaction of colchicine with certain prescription drug products. (*See id*. at 681-82.) It also looked at the drug-drug interaction studies that West-Ward submitted with its Mitigare approval application—studies that, quite surprisingly, had come to the *opposite* conclusion about whether health problems were likely to arise when a person taking certain inhibitor medications also takes colchicine for the prophylaxis of gout. (*See id*. at 668, 692-94). Ultimately, in a memo entitled "The Curious Case of Colchicine: What to Do About Conflicting Drug Interaction Study Results for the Same

Molecular Entity" (*id*. at 667-672), Michelle Garner, who was the Senior Regulatory Management Officer, represented the conclusion of a "regulatory briefing panel" of FDA research scientists about what information needs to be conveyed regarding drug-drug interactions: the panel determined both that "in light of the new information provided by the West-Ward DDI studies, and the questions about the generalizability of dose modification recommendations, . . . it was reasonable to forego detailed dose modification recommendations," and also that "a general precaution to reduce the daily dose and monitor closely for colchicine toxicity is reasonable[.]" (*Id*. at 672).[26] Given that FDA never promised in the Colchicine Citizen Petition Response to require that Colcrys's drug-drug interaction table appear on all future products, and also that the agency *did* engage in precisely the kind of individualized assessment of Mitigare's label that the Colchicine Citizen Petition Response said would be required regarding single-ingredient oral colchicine products in the future, FDA's conclusion that Mitigare did not need to include the same low-dose requirements as appear on Colcrys's label was

[26] According to Takeda, FDA's acceptance of a more general warning in lieu of Colcrys's specific drug-drug interaction table marked a capricious return to the "pre-Colcrys wild, wild west world of 'we have no information about this drug.'" (*See* PI Mot. Hr'g Tr. at 40:5-6.) But there is a significant difference between what Mitigare's label says about drug-drug interactions and the information that colchicine products conveyed on this subject back in the days prior to FDA regulation. (*Compare* AR at 19 (describing pre-Colcrys warnings as no more than "avoidance when possible and caution when necessary, with vigilant monitoring of clinical signs of toxicity") *with* AR at 32, 33, 34-35, 38-39 (Mitigare label repeatedly explaining the potential toxicities that can result from the interaction of colchicine and certain other products and describing the four drug-drug interaction studies conducted by West-Ward).) Furthermore, rather than indicating the agency's intent to retreat to "the old, pre-Colcrys regime that had resulted in unnecessary toxicity and deaths" (Takeda Reply Mem. at 15), the record clearly demonstrates that the general warnings on Mitigare's label were instead largely motivated by doubts that FDA scientists had developed regarding *Mutual's* findings based on West-Ward's more recent research. (*See* AR at 672 ("The panel agreed that the West-Ward DDI studies raise questions about the generalizability of detailed dose modification recommendations to drugs that have not been directly studied and asked the team whether safety concerns had arisen based on the detailed dose modification recommendations in the Colcrys labeling. . . . *There was some discussion of whether the Colcrys labeling should be revised*." (emphasis added).)

hardly a change of FDA's position, much less an "arbitrary" or "capricious" deviation from its prior policy.

A closer question is presented when one considers a statement that FDA made in the Colchicine Citizen Petition Response regarding Mutual's AGREE Trial results and the extent to which the labels of future single-ingredient oral colchicine products approved for the prophylaxis of gout flares must provide information about the use of the product for the treatment of acute gout flares. In the Citizen Petition Response, FDA considered whether the labels of single-ingredient oral colchicine products must alert health care providers to the possibility that a low-dose regimen of oral colchicine could be safely added to treat the acute gout flares of a person who is regularly taking oral colchicine for prophylaxis of gout. As explained in Part I.C.1, *supra*, Mutual had studied precisely how much additional colchicine could be added to a regular oral colchicine regimen to treat an acute gout flare in its AGREE Trial, and Colcrys was specifically approved for the treatment of acute gout flares on the basis of the AGREE Trial data. FDA did specifically state in the Colchicine Citizen Petition Response that "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" (AR at 3); yet, as Takeda points out, FDA did not require the AGREE trial information to appear on Mitigare's label. (Takeda PI Mem. at 27-28.) To the extent that FDA's decision to approve Mitigare without a label that included Colcrys's AGREE trial regimen can be viewed as a departure from the agency's prior position, this Court concludes that it was not an unreasoned change in

position in violation of the APA (*see* Takeda PI Mem. at 26-29), because the record clearly reflects the agency's well-reasoned and well-supported rationale for reaching this conclusion.

Specifically, it is clear that FDA focused primarily on the undisputed fact that West-Ward had submitted an application for approval of its colchicine capsule solely for *prophylaxis* of gout. In fact, West-Ward expressly disclaimed that Mitigare should be indicated for the treatment of acute gout flares. (*See* AR at 28, 51). With this in mind, when the agency considered whether the product's packaging nevertheless needed to include the specific lower-dose regimen instructing patients how to use oral colchicine safely for the treatment of gout acute flares that Mutual developed based on the AGREE Trial and that appears on Colcrys's label, the agency came to the utterly rational conclusion that a label with the lower-dose instructions was not only unwarranted, it might also confuse users into taking more Mitigare than the recommended daily dosage, exposing them to greater risk of harm. (*See id.* at 113.) What is more, FDA was fully aware that the medical community largely discourages patients who are taking oral colchicine for the ongoing prophylaxis of gout to take additional oral colchicine for the treatment of a gout flare—other medications are typically prescribed for this purpose. (*See id.* at 4, 817; *see also* Mot. Hr'g Tr. Nov. 4, 2014 (hereinafter, "PI Mot. Hr'g Tr.") at 57:23-58:5). This meant that requiring West-Ward to include on Mitigare's label instructions for adding doses of colchicine to treat an acute gout flare would send exactly the wrong message about how the product should be use and for what purpose. FDA scientist Dr. Sarah Yim explained the agency's reasoning this way:

> It is well-recognized that recent colchicine use (*i.e.*, for prophylaxis of gout flares) increases the susceptibility to toxicity related to additional doses of colchicine. Although the applicant 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.

(AR at 113 (emphasis added).) Thus, as approved, the Mitigare label proclaims that "[t]he safety and effectiveness of Mitigare for acute treatment of gout flares during prophylaxis has not been studied" (*id*. at 32), and the Mitigare Medication Guides instructs patients that "[i]f you have a gout flare while taking Mitigare, tell your healthcare provider" (*id*. at 43).

In light of the agency's clear and convincing record statements about why it permitted the Mitigare label to differ from that of Colcrys, it is puzzling that Takeda puts so much stock into trying to persuade the Court that FDA somehow failed to explain its decisions regarding Mitigare's label adequately. To this end, Takeda complains that FDA has not sufficiently articulated its reasons for approving a Mitigare label that omitted specific, known information about the drugs that Takeda had studied (*see* Takeda Reply Mem. at 11-12), and it suggests that the agency was not justified in refusing to require inclusion of Mutual's findings *in addition to* West-Ward's, along with an explanatory statement that the Colcrys research findings might not be generalizable (*see id*.). Takeda also presses the argument that FDA needed to say more than it did regarding its decision to jettison the AGREE trial's lower dose regimen for the treatment of acute gout flares, which, according to Takeda, was a must-have item for Mitigare's label in light of the agency's "own regulations, which specifically

acknowledge that risk information related to common 'off label uses' may be required in labeling." (Takeda Reply Mem. at 9 (citing 21 C.F.R. § 201.57(c)(6)). Of course, by the plain terms of these same regulations (specifically, the "may") the agency has discretion regarding whether or not to require a product's label to include information related to off-label uses. *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" (emphasis added)). Moreover, as far as the APA is concerned, it is well established that just because the agency *could* have chosen to require West-Ward to adopt the Colcrys label (or parts thereof) does not mean that the agency *had* to do so. *See, e.g.*, *Hospira, Inc. v. Burwell*, 2014 WL 4406901, at *17 (D. Md. 2014) ("FDA is not obligated to consider how the product *might* be used by physicians beyond the approved labeling." (emphasis in original)).

In any event, under the relevant review standard, this Court has no choice but to defer to "the agency['s] . . . choice between rational alternatives." *Rempfer v. Von Eschenbach*, 535 F. Supp. 2d 99, 107 (D.D.C. 2008) (citing *Alliance for Bio–Integrity v. Shalala*, 116 F. Supp. 2d 166, 177 (D.D.C. 2000) *aff'd sub nom. Rempfer v. Sharfstein*, 583 F.3d 860 (D.C. Cir. 2009)). Here, FDA determined that the recent scientific research about the interaction between colchicine and certain classes of inhibitor drugs cast doubt on the generalizability of Mutual's drug-drug interaction studies, so the agency thought it best not to require that the detailed Colcrys tables be included on Mitigare's label. In addition, the agency made the entirely rational decision that

instructions about the additional low-dose amounts that a user might take for the treatment of gout flares were inappropriate for Mitigare, given that Mitigare was being approved solely for the prophylaxis of gout flares.[27] The record demonstrates that FDA employed its scientific expertise to reach these reasoned conclusions about Mitigare's label, and the agency showed its work, in the form of various memos detailing its considerations and conclusions in this regard. Takeda has not established that the APA requires anything more.

C. FDA's Decision To Approve Mitigare With A Label That Contains Safety Information That Differs From Colcrys Was Not Arbitrary And Capricious

Finally, Takeda attempts to cast the dissimilarity between the Mitigare and Colcrys labels in a slightly different light, by arguing that FDA's approval of Mitigare was arbitrary and capricious because, "[a]s approved, Mitigare is not safe in light of the significant deficiencies in its labeling." (PI Takeda Mem. at 30 (citing *Food and Drug Admin. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000).) On its face, this contention suggests that Takeda believes FDA was *mistaken* in its ultimate determination that Mitigare is safe and effective (a hard contention to make for a drug manufacturer that also maintains that its own drug product is substantively identical to the drug it challenges); as it turns out, however, Takeda's actual argument appears to be that, in light of the long history of adverse events related to colchicine toxicity, a 0.6 milligram single-ingredient oral colchicine product simply *cannot* be safe and effective

[27] West-Ward points out that Colcrys's lower dose regimen for acute gout flares also simply cannot be achieved, as a practical matter, with Mitigare's capsule product. (*See* PI Hr'g Tr. at 51-52 ("[T]he specific dose adjustment in the Colcrys label often are .03 milligrams. Colcrys is a .6-milligram tablet. The only way you get to .3 milligrams is you have to split the tablet. You can't do that with [West-Ward]'s Mitigare, because our product is a capsule. You can't split a capsule. Everything will fall apart.").) This fact, too, supports the rationality of FDA's conclusion that the lower dose information need not be included on Mitigare's label.

without a label that contains the low-dose regimen for treating acute gout flares and the drug-drug interaction information that is part of the Colcrys package. (Takeda PI Mem. at 30-32.) Of course, as explained in some detail in the previous section, FDA has specifically determined otherwise. Raised again in this context, Takeda's safety concerns essentially invite this Court to disagree with FDA's underlying scientific judgments about whether it is necessary to include the Colcrys label information on Mitigare's label.

That request will not be honored. As explained above, on this record, Takeda cannot reasonably maintain that FDA made a "clear error" of administrative judgment when it decided to permit Mitigare to be marketed with a label that differs from Colcrys. *Overton Park*, 401 U.S. at 416. Furthermore, the agency's scientific determination that Mitigare is safe and effective as labeled is entitled to the highest degree of deference, meaning that, even if this Court had the expertise to reevaluate FDA's safety and efficacy decision, it could not freely supplant the agency's scientific judgments about what a drug product's label must include in order to ensure safe use of that product, any more than it could roll up its sleeves and dig into the data or run its own clinical experiments in order to determine whether FDA was wrong to conclude that such drug product was, in fact, safe. FDA is the administrative body that has both the expertise and the authority to evaluate the safety and efficacy of drugs, and its conclusion that a drug product submitted to it for approval—including a product with a label that differs substantially from one that is already on the market—is safe and effective must be respected. *See Sanofi-Aventis U.S. LLC v. FDA*, 842 F. Supp. 2d 195, 209 (D.D.C. 2012) ("[D]eference is particularly appropriate when FDA approval of

drugs is involved") (citing *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1324 (D.C. Cir. 1998)); *see also 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") (citing *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)); *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 falls squarely within the ambit of the FDA's expertise and merit deference from us."); *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.").

Applying the necessary deference here, this Court adopts its own findings about the rationality of FDA's decisions regarding Mitigare's label that are the discussion in the previous section, and the bases for them (*i.e.*, it concludes that Takeda's challenge fails because FDA fully explained its conclusion that Mitigare meets the applicable safety standards as labeled, and that explanation appears to be reasonable).

III. CONCLUSION

When it established the Section 505(b)(2) new drug approval process as part of the Hatch-Waxman Amendments to the FDCA, Congress placed the burden of proving that a new drug product is safe and effective squarely on the Section 505(b)(2) applicant, and it charged FDA with the responsibility of determining whether that burden has been carried as a scientific matter and, thus, whether a new drug may be marketed. Although Plaintiffs here maintain that FDA's drug-approval duties carry with them the responsibility of ensuring that third-party patent rights are protected, nothing in the FDCA or the agency's procedural rules required FDA to force West-Ward to reference Colcrys and to certify to its patents under the circumstances presented here, because (1) West-Ward's Mitigare is not a duplicate of Colcrys, and (2) West-Ward did not rely upon Colcrys data or FDA's findings of safety and effectiveness with respect to Colcrys in order to support the Mitigare Section 505(b)(2) new drug application. Moreover, it is clear from the administrative record that FDA's decision to approve Mitigare with a label that differs from Colcrys was well-supported, and that FDA's determination was not unreasonable, unwarranted, or unexplained.

Accordingly, as set forth in the separate order that was issued on January 9, 2015, the Plaintiff Takeda Pharmaceuticals U.S.A., Inc.'s Motion for Summary Judgment in *Takeda Pharms. U.S.A., Inc. v. Burwell, et al.*, Civ. No. 14-1668-KBJ (D.D.C. Oct. 6, 2014) is **DENIED**; Plaintiffs Elliott Associates, L.P., Elliott International, L.P., Knollwood Investments, L.P.'s Motion for Summary Judgment in *Elliott Assocs., et al. v. Burwell, et al.*, Civ. No. 14-1850-KBJ (D.D.C. Nov. 4, 2014), is **DENIED**; and Defendants' and Defendant-Intervenors' cross-motions for summary

judgment in *Elliott Assocs., et al. v. Burwell, et al.*, Civ. No. 14-1850-KBJ (D.D.C. Nov. 4, 2014), are **GRANTED**.

DATE: January 13, 2015

Ketanji Brown Jackson
KETANJI BROWN JACKSON
United States District Judge