[ORAL ARGUMENT NOT YET SCHEDULED]

Nos. 15-5021 & 15-5022

IN THE UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

TAKEDA PHARMACEUTICALS U.S.A., INC.,
ELLIOTT ASSOCIATES, L.P., ELLIOTT INTERNATIONAL, L.P., and
KNOLLWOOD INVESTMENTS, L.P.,

Plaintiffs-Appellants,

v.

SYLVIA MATHEWS BURWELL, in her official capacity as Secretary, United States Department of Health and Human Services, et al.,

Defendants-Appellees,

HIKMA PHARMACEUTICALS PLC and
WEST-WARD PHARMACEUTICALS CORP.,

Intervenors-Appellees.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

BRIEF FOR APPELLEES

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CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES

Pursuant to D.C. Circuit Rule 28(a)(1), the undersigned counsel certifies:

A. Parties and Amici. The appellants are Takeda Pharmaceuticals U.S.A., Inc., Elliott Associates, L.P., Elliott International, L.P., and Knollwood Investments, L.P. With this Court's permission, Hikma Pharmaceuticals PLC and West-Ward Pharmaceuticals Corp. intervened in support of the appellees.

With the consent of the parties, Pharmaceutical Research and Manufacturers of America participates as amicus curiae in support of the appellants, and Generic Pharmaceutical Association participates as amicus curiae in support of the appellees.

B. Rulings Under Review. These cases are appeals from the United States District Court for the District of Columbia. Appellants seek review of the district court's orders granting the government's motions for summary judgment and upholding FDA's approval of a new drug application submitted by intervenors Hikma Pharmaceuticals PLC and West-Ward Pharmaceuticals Corp. *Elliott Associates, L.P. v. Burwell*, No. 14-cv-1850 (Jan. 9, 2015) (Hon. Kentaji Brown Jackson); *Takeda Pharmaceuticals U.S.A., Inc. v. Burwell,* No. 14-cv-1668 (Jan. 15, 2015) (Hon. Kentaji Brown Jackson).

C. Related Cases. We are not aware of any other related cases within the meaning of D.C. Circuit Rule 28(a)(1)(C).

Respectfully submitted,

/s/ Sonia K. McNeil

TABLE OF CONTENTS

Page(s)

TABLE OF AUTHORITIES

Cases: **Page(s)**

Statutes:

* Authorities chiefly relied upon are marked with an asterisk.

Regulations:

Legislative Materials:

Other Authorities:

GLOSSARY

AGREE trial	Acute Gout Flare Receiving Colchicine Evaluation trial
ANDA	Abbreviated New Drug Application
FDCA	Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301 *et seq.*
JA	Joint Appendix
NDA	New Drug Application

INTRODUCTION

These appeals challenge the Food and Drug Administration's decision to approve a new drug application submitted by intervenors West-Ward Pharmaceuticals Corp. and Hikma Pharmaceuticals PLC (collectively, "West-Ward") for Mitigare, a drug to treat gout flares prophylactically. Mitigare contains colchicine, a substance that has been used for many centuries to treat gout, and used to prevent gout flares since before the enactment of the modern Federal Food, Drug, and Cosmetic Act. Appellants Takeda and Elliott market Colcrys, a drug that contains colchicine and is approved for prophylaxis of gout flares, as well as treatment of acute gout flares. FDA's approval of Mitigare threatens the market for Colcrys.

These appeals are half of a two-part effort to keep Mitigare off the market. Before a different court, Takeda sued West-Ward for patent infringement. That court denied a preliminary injunction, the Federal Circuit affirmed, and West-Ward's motion to dismiss Takeda's complaint is pending. In this suit, Takeda and Elliott claim that FDA's decision to approve Mitigare violated the Administrative Procedure Act. Takeda and Elliott both argue that FDA should have required West-Ward to file a certification regarding the relationship between Mitigare and patents covering Colcrys before FDA approved Mitigare, though they disagree about why FDA should have done so. Takeda also asserts that FDA's choice of language for Mitigare's label is inconsistent with prior statements by FDA.

The district court correctly rejected these claims. As the court explained, the patent certification requirements invoked by Takeda and Elliott only attach to drugs on whose finding of safety and efficacy by FDA the applicant relies for approval of its own application. West-Ward's application for Mitigare did not rely on FDA's finding of safety and effectiveness for Colcrys, and the FDCA therefore did not require West-Ward to make a certification regarding the patents applicable to Colcrys. The district court also correctly concluded that FDA's choices regarding Mitigare's label were reasonable and well supported by the record. The judgment of the district court should be affirmed.

STATEMENT OF JURISDICTION

This is a civil action involving claims arising under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act. The district court entered final judgment in favor of the government on January 15, 2015. Appellant Takeda Pharmaceuticals U.S.A., Inc. ("Takeda"), filed a timely notice of appeal in this Court on January 26, 2015 (No. 15-5021). Appellants Elliott Associates, L.P., Elliott International, L.P., and Knollwood Investments, L.P. (collectively, "Elliott") filed a timely notice of appeal in this Court on January 26, 2015 (No. 15-5022). This Court has jurisdiction under 28 U.S.C. § 1291.

STATEMENT OF THE ISSUES

1. Whether the district court correctly concluded that FDA's decision to approve Mitigare without requiring West-Ward to file a Paragraph IV certification to Colcrys is consistent with the FDCA and FDA regulations and policy.

2. Whether the district court correctly concluded that FDA's choice of language for Mitigare's label is consistent with prior statements by FDA.

PERTINENT STATUTES AND REGULATIONS

Pertinent statutes and regulations are reproduced in the addendum to this brief.

STATEMENT OF THE CASE

I. STATUTORY AND REGULATORY BACKGROUND

The Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301 *et seq.*, makes it unlawful to introduce new drugs into interstate commerce without prior approval by the Food and Drug Administration (FDA). *Id.* §§ 331(d), 355(a). To obtain premarket approval, an applicant must demonstrate, *inter alia*, that the new drug is safe and effective for its intended uses. *Id.* § 355(d)(1)-(2), (4)-(5).

Prior to 1984, the only means of obtaining premarket approval was through the submission of a New Drug Application (NDA). 21 U.S.C. § 355(b)(1). Before submitting an NDA, an applicant must undertake clinical investigations to demonstrate the safety and effectiveness of the new drug, and the NDA must include the results of those investigations. *Id.* § 335(b)(1)(A). The NDA requirements applied both to "pioneer" drugs and to generic drugs. Thus, even if a generic drug was

identical to a previously approved pioneer drug in all relevant respects, the generic manufacturer had to generate and submit independent clinical data regarding the drug's safety and effectiveness.

In 1984, Congress revised the FDCA's premarket approval provisions by enacting the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, commonly known as the Hatch-Waxman Amendments. Congress enacted the Hatch-Waxman Amendments with the goals of encouraging innovation in the development of new drugs, fostering competition among drug manufacturers, and accelerating the availability to consumers of lower-cost alternatives to expensive brand-name drugs. *See* H.R. Rep. No. 98-857 (Part I), at 14-15 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647-2648.

The Hatch-Waxman Amendments created two new regulatory pathways for premarket approval of new drugs: the Abbreviated New Drug Application (ANDA) and the "505(b)(2) application." *See generally Eli Lilly & Co. v. Medtronic Inc.*, 496 U.S. 661, 676 (1990). Both pathways permit the applicant to rely on FDA's finding of safety and effectiveness for a previously approved drug, thereby minimizing or eliminating the time and expense associated with clinical investigations, and reducing the length of the premarket approval process.

If an applicant is seeking approval for a generic version of a pioneer drug, the applicant may submit an ANDA, which must demonstrate that the applicant's drug is the same as the pioneer drug in all relevant respects; the applicant may then rely solely

on FDA's findings about the pioneer drug's safety and effectiveness. 21 U.S.C. § 355(j)(2)(A). If an applicant is seeking approval for a drug that shares some characteristics (*e.g.*, active ingredient, dosage form, or strength) with a previously approved drug but is different from that pioneer drug in other respects, the applicant may submit a 505(b)(2) application, which may rely wholly or partially on FDA's findings about the prior product's safety and effectiveness. *Id.* § 355(b)(2). A 505(b)(2) applicant must also submit supplemental data to show that its proposed drug meets the statutory standard for safety and effectiveness notwithstanding any differences between the proposed drug and the previously approved drug on whose finding of safety and effectiveness the applicant chooses to rely. *See ibid.*

A 505(b)(2) applicant must submit a certification "with respect to each patent which claims the drug for which" the investigations "relied upon by the applicant for approval of the application" "were conducted," as well as for each patent "which claims a use for such drug for which the applicant is seeking approval." 21 U.S.C. § 355(b)(2), (b)(2)(A). With respect to each such patent, the applicant must certify that (1) the patent information has not been filed with FDA; (2) the patent has expired; (3) the applicant is not requesting approval of the drug until after the patent has expired; or (4) the patent is invalid or would not be infringed by the applicant's drug. *Id.* § 355(b)(2)(A)(i)-(iv), (c)(3)(A)-(C); *see also id.* § 355(j)(2)(A)(vii)(I)-(IV), (j)(5)(B) (same certification requirements for ANDAs). FDA may not approve an application that lacks a required certification. *Id.* § 355(d)(6), (j)(4)(J).

The regulatory timetable for approval of 505(b)(2) applications and ANDAs is dictated, in part, on whether a previously approved drug on which an applicant relies is protected by patents listed with FDA. An applicant who certifies that the patent is invalid or would not be infringed (a "Paragraph IV" certification) must notify the NDA holder and each patent holder "not later than 20 days after * * * the application has been filed." 21 U.S.C. § 355(b)(3), (j)(2)(B); *see also* 21 C.F.R. § 314.95(b) (providing that "[t]he applicant shall send the notice * * * when it receives from FDA" a letter acknowledging receipt of the application). The applicant's notice must explain in detail "the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed." 21 U.S.C. § 355(b)(2)(D)(ii).

The filing of a Paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is treated as an act of patent infringement. 35 U.S.C. § 271(e)(2)(A). If the patent holder or exclusive patent licensee sues for infringement within 45 days of receiving the notice, FDA must stay approval of the 505(b)(2) application or ANDA for 30 months from the date that any patent holders received notice or until certain other events occur, such as a court reaching judgment in the patent litigation. 21 U.S.C. § 355(c)(3)(C), (j)(5)(B)(iii).

II. FACTUAL AND PROCEDURAL BACKGROUND

A. Colchicine

Colchicine is derived from the *Colchicum autumnale* plant. It has been used to treat gout for centuries. JA215; JA749. Colchicine has been used for prophylactic

treatment of gout flares since the 1930s, before the enactment of the FDCA. JA750. Single-ingredient oral colchicine tablets in 0.6 mg strength have been available to consumers as unapproved drugs for decades. *Ibid.*

Colchicine has long been known to be toxic to humans when used outside of a narrow range of doses. JA749. Generally speaking, patients consuming higher doses of colchicine are at greater risk of developing colchicine toxicity. For more than forty years, scientific literature has recognized that colchicine may interact with certain other drugs in ways that increases colchicine's potential toxicity. JA898.

In 1961, FDA approved a drug named ColBenemid as safe for use to prevent acute gout flares. JA750. ColBenemid combined colchicine and a substance called probenecid. *Ibid.* Soon after, Congress amended the FDCA to require that drugs be proven to be effective as well as safe for their intended uses. Pub. L. No. 87-781, 76 Stat. 780 (1962). FDA subsequently concluded that ColBenemid was effective for the prevention of acute gout flares. *See* 37 Fed. Reg. 15,189 (July 28, 1972); JA25. In 1976, FDA approved a generic equivalent of ColBenemid called Col-Probenecid, which remains on the market. JA25. Col-Probenecid is not patented. JA37-38.

B. Colcrys

1. In 2006, FDA launched an effort to remove from the market unapproved drugs that, for historical reasons, were nonetheless available to consumers. JA26-31. Manufacturers of unapproved colchicine drug products, including West-Ward and Mutual Pharmaceutical Company, Inc. ("Mutual"), the predecessor of appellant

Takeda, subsequently removed their products from the market. JA31-32. Both manufacturers sought FDA's approval to resume marketing their products. JA32.

As relevant here, Mutual submitted two 505(b)(2) applications seeking approval of a 0.6 mg single-ingredient oral colchicine tablet to be marketed under the name Colcrys. JA32. One application sought approval to market Colcrys for the treatment of acute gout flares. JA33-35. That application relied on FDA's findings about the safety and effectiveness of Col-Probenecid and on published literature on colchicine. JA33. To compensate for a dearth of evidence about the use of colchicine to treat acute gout flares, Mutual also submitted data from its Acute Gout Flare Receiving Colchicine Evaluation (AGREE) trial. *Ibid.* The results of this trial supported the use of low doses of colchicine to treat acute gout flares. JA34. FDA approved Colcrys for the treatment of acute gout flares in July 2009. JA34-35. The AGREE trial was essential to the approval of Colcrys for treatment of acute gout flares; as a result, FDA granted Colcrys a 3-year period of exclusivity for the treatment of acute gout flares, which expired on July 30, 2012. *See* 21 U.S.C. § 355(c)(3)(E)(iii).

Mutual's application to use colchicine to treat acute gout flares also included studies on the risk of toxicity caused by the interaction of colchicine with certain drugs that inhibit certain enzymes, and thus change how the human body processes colchicine. JA34. Though the potential for such harmful interaction was already well known, Mutual's studies supported a more precise colchicine dosage adjustment. *Ibid.* Mutual's labeling generally recommended that patients taking Colcrys to treat acute

gout flares while also taking certain enzyme inhibitors should reduce the number of whole Colcrys tablets consumed. *See* JA134-135.

Mutual's other application sought to market Colcrys for use in preventing gout flares. JA35-36. This application relied on both published literature on colchicine and FDA's finding that Col-Probenecid was safe and effective for gout flare prophylaxis, and cross-referenced Mutual's earlier application. *Ibid.* Mutual's labeling generally urged patients taking Colcrys for prophylaxis of gout flares along with enzyme inhibitors to reduce their periodic Colcrys dosage from one tablet (0.6 mg) to one-half tablet (0.3 mg). JA134-135. FDA approved Colcrys for gout flare prophylaxis in October 2009. JA34-35.

Mutual listed seventeen patents with FDA on methods of using colchicine, the earliest of which expires in October 2028. JA30; JA506-507. Some of these patents cover methods of using colchicine to treat acute gout flares and methods of using colchicine for prophylaxis of gout flares in patients who also take certain enzyme inhibitors. JA530-531 ¶ 22(A)-(E). After FDA approved Colcrys, the drug's price increased more than 50-fold. JA216-17; JA1030-1031; *Mutual Pharmaceutical Co. v. Watson Pharmaceuticals, Inc.*, 2009 WL 3401117, at *1 (C.D. Cal. Oct. 19, 2009).

2. On the same day that FDA approved Colcrys for treatment of acute gout flares, the agency issued an "FDA Alert" to healthcare professionals. JA34-35; JA126-128. The Alert noted that Mutual's studies had shown that low doses of colchicine were effective to treat acute gout flares and recommended that healthcare

professionals follow FDA's approved Colcrys dose, rather than administering "the higher dose traditionally used." JA126.

FDA also observed that its analysis of "safety data for colchicine from adverse events reported to the Agency, the published literature, and company-sponsored pharmacokinetic and drug interaction studies" had revealed new information about colchicine toxicity. JA126. FDA encouraged healthcare professionals treating patients with colchicine to avoid prescribing certain enzyme inhibitors, to reduce or stop colchicine treatment, or to refer to the Colcrys labeling "for specific dosing recommendations and additional drug interaction information." *Ibid.*

Roughly one year later, FDA announced that the agency intended to pursue enforcement action against marketers of unapproved colchicine products. 75 Fed. Reg. 60,768 (Oct. 1, 2010). FDA's announcement noted that "a new clinical trial in acute gout * * * found that a lower dose of oral colchicine than had been considered the standard of care was just as effective for the treatment of an acute gout flare, and resulted in fewer adverse effects." *Id.* at 60,769. The notice also observed that "specific dose modification and reduction recommendations" in "recently approved colchicine labeling" reflected the agency's latest analysis of the risks associated with interactions between colchicine and other drugs. *Ibid.* "Because FDA has not approved the labeling for unapproved single-ingredient colchicine products," the agency explained, "their labeling likely does not contain appropriate dosing and drug interaction information" or "reflect the most current data." *Ibid.*

C. Mutual's Citizen Petition and FDA's Response

In August 2010, West-Ward submitted a 505(b)(2) application seeking approval of a 0.6 mg single-ingredient oral colchicine tablet for prophylaxis of gout flares. JA37-38. Like Mutual's application for gout flare prophylaxis, West-Ward's application relied on FDA's finding that Col-Probenecid was safe and effective for gout prophylaxis and on published literature on colchicine. *Ibid.* West-Ward did not rely on FDA's finding of safety and effectiveness for Colcrys and did not file a certification to Colcrys patents. *Ibid.*

Mutual learned of West-Ward's application and, in November 2010, filed a citizen petition with FDA. *See generally* 21 C.F.R. § 10.30 (citizen petition provisions). As relevant here, 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." JA39; JA175-196 (Mutual petition).

[redacted].

In May 2011, FDA granted the petition in part and denied it in part. JA472-498. FDA agreed with Mutual that manufacturers whose products duplicated Colcrys exactly should seek approval through the ANDA process. JA473-474; JA482-487. FDA also agreed 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." JA474; JA490-491. But FDA declined to require any 505(b)(2) application for a single-ingredient colchicine product to rely on Colcrys "irrespective of whether the proposed product shares the same strength, pharmacokinetic (PK) profile, or other characteristics such as dosage form or conditions of use." JA474; JA487-492. "Whether 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," FDA explained. JA492.

D. Mitigare

1. [redacted]

[redacted]; *cf.* 21 C.F.R. § 314.105(c) ("FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug.").

[redacted].

2. In October 2012, West-Ward submitted a new 505(b)(2) application for a 0.6 mg single-ingredient oral colchicine capsule for gout flare prophylaxis called Mitigare. JA41. Because the proposed product was a capsule, not a tablet, Mitigare did not duplicate an existing drug and West-Ward did not seek approval through the ANDA process. *See* 21 U.S.C. § 355(j)(2)(A)(iii) ("An abbreviated application for a new drug shall contain * * * information to show" that "the dosage form" is "the same" as the previously approved product).

West-Ward's new 505(b)(2) application relied on FDA's finding about Col-Probenecid and published literature on colchicine to support the safety and efficacy of Mitigare for gout prophylaxis. JA41-43; JA710. To develop its own dosage recommendations, West-Ward conducted four new studies of the interaction of colchicine and drugs that inhibit certain enzymes in varying degrees, and submitted the resulting data with its 505(b)(2) application. JA41-42; JA718.

FDA conducted a thorough review of West-Ward's application. *See* JA708-774; JA775-781; JA782-831; JA839-884; JA894-945. The agency ultimately concluded that West-Ward's application provided adequate evidence of the safety and effectiveness of colchicine to treat gout flares prophylactically. *See* JA760-764; JA779-780; JA797-825. As FDA observed, "colchicine is a well-known drug and the efficacy and safety of colchicine in gout is well accepted." JA780.

West-Ward's studies "generated new insights" about the interaction of colchicine with enzyme-inhibiting drugs, however. JA720-722. "Unexpectedly," West-Ward's studies suggested that a patient's colchicine dose need not be adjusted to avoid harmful interaction with certain enzyme inhibitors, in apparent tension with the results of Mutual's drug-drug interaction studies. JA42; JA749; JA894-899. After extensive analysis, *e.g.*, JA720-735; JA756-759; JA778-779; JA894-945, [redacted]

[redacted]

On the basis of all the evidence, FDA determined that Mitigare's labeling should warn that Mitigare should not be combined with certain drugs or, if combinations could not be avoided, that the patient's doctor should consider reducing the patient's colchicine dose and "the patient should be monitored carefully for colchicine toxicity." JA43; JA699-700; JA781; *see also* [redacted]. Since FDA did not approve Mitigare to treat acute gout flares, FDA reasoned that Mitigare's label should state among the "[l]imitations of use" that "[t]he safety and effectiveness of Mitigare for acute treatment of gout flares during prophylaxis has not been studied." JA43; JA699. FDA approved Mitigare for gout flare prophylaxis in September 2012. JA695-697.

E. Prior Proceedings

Following FDA's decision, West-Ward announced the approval of Mitigare and declared its intent to market a generic version of Mitigare at lower cost than Colcrys. JA43-44; JA522. Takeda then filed two lawsuits against West-Ward. One suit asserted that Mitigare infringed Takeda's Colcrys patents. The second suit, which is

the subject of this appeal, asserted that FDA had violated the APA by approving Mitigare. Elliott, which has a financial interest in Colcrys, filed a similar APA challenge against FDA.

1. *Patent Litigation.* a. Takeda filed its patent infringement suit in the United States District Court for the District of Delaware on October 3, 2010. JA524-541. Takeda sought a declaratory judgment of patent infringement against West-Ward, on the theory that West-Ward "actively induces infringement" of Takeda's patents on methods of using colchicine for acute gout flares because West-Ward "knows and intends that patients" using Mitigare to treat gout prophylactically "will also use" Mitigare to treat acute gout flares, and West-Ward "will make no effort to stop" such behavior. JA533-534 ¶¶ 33-34; *see* 35 U.S.C. § 271(b). Takeda further claimed that West-Ward "actively induces infringement" of Takeda's patents on methods of using colchicine in patients taking enzyme inhibitors because West-Ward "knowingly intend[s]" that "doctors and patients will inevitably have to consult the dose regimens set forth" in the Colcrys label to use Mitigare safely and effectively, as evidenced by the fact that Mitigare's label "fails to specify how to reduce the dose or dose frequency" to avoid harmful drug-drug interaction. JA534 ¶¶ 35-36. Takeda requested a preliminary injunction barring West-Ward from marketing Mitigare or its generic equivalent.

On November 4, 2014, after entering a temporary order to preserve the status quo, the district court denied Takeda's request for a preliminary injunction. Mem.

Op., *Takeda Pharmaceuticals U.S.A., Inc. v. West-Ward Pharmaceutical Corp.*, No. 14-1268 (D. Del. Nov. 4, 2014). "[G]iven the significance of this dispute to both parties," the court offered to maintain its temporary order if Takeda immediately appealed and requested expedited review. *Id.* at 15. Takeda did so, and West-Ward cross-appealed.

b. In January 2015, after oral argument, the Federal Circuit affirmed the district court's order denying Takeda's motion for a preliminary injunction, vacated the district court's order preserving the status quo, and dismissed as moot West-Ward's cross-appeal. Order, *Takeda Pharmaceuticals U.S.A., Inc. v. West-Ward Pharmaceutical Corp.*, Nos. 2015-1139, 2015-1142 (Fed. Cir. Jan. 9, 2015). The appellate court noted that "[t]he consequence * * * is that both parties are free to immediately offer colchicine products for prophylactic use." *Id.* at 2.

In May 2015, the Federal Circuit issued an opinion explaining its reasoning. *Takeda Pharmaceuticals U.S.A., Inc. v. West-Ward Pharmaceutical Corp.*, Nos. 2015-1139, 2015-1142 (Fed. Cir. May 6, 2015). Addressing Takeda's patents on the use of Colcrys to treat acute gout flares, the court explained that Takeda could not prove induced infringement through "vague label language * * * combined with speculation about how physicians may act." Slip op. at 12. Further, "even if we do look outside the label, there is no evidence that the label would necessarily lead doctors who are consulted by patients taking Mitigare to prescribe an off-label use of it to treat acute gout flares." *Id.* at 13; *see also id.* at 8-16 (explaining the deficiencies of Takeda's submissions). As for the other patents, the Federal Circuit agreed that Takeda failed

to show that doctors and patients would act as Takeda predicted; "[s]ince there was insufficient proof of direct infringement here," the appellate court explained, "we need not reach the question of whether there was evidence of inducement." *Id.* at 18; *see also id.* at 16-18 (rejecting Takeda's arguments). Takeda filed a petition for en banc rehearing, which the Federal Circuit denied in August 2015.

c. In September 2015, Takeda filed an amended complaint in the United States District Court for the District of Delaware. On October 1, 2015, West-Ward moved to dismiss Takeda's amended complaint for failure to state a claim. As of this date, the district court has not ruled on West-Ward's motion.

2. *APA Litigation.* On October 6, 2014, days after filing the patent suit, Takeda filed its APA suit in the United States District Court for the District of Columbia. JA99-124. Elliott filed its APA suit in the same court on November 4, 2014. JA445-466. As relevant here, Takeda and Elliott argued that FDA violated the FDCA and FDA regulations and policy by approving Mitigare without requiring West-Ward to submit a Paragraph IV certification to Colcrys. Takeda also asserted that FDA ignored agency precedent by approving Mitigare without requiring that Mitigare's label list specific dosage adjustments for patients taking enzyme inhibitors and information about the efficacy of low doses of colchicine to treat acute gout flares.

The district court consolidated the cases and treated the parties' filings as cross-motions for summary judgment. JA22. The court granted summary judgment to the government. In a lengthy and painstaking opinion, the court rejected each of the

plaintiffs' arguments. JA18-97. The district court concluded that it was "clear" that FDA had acted lawfully in approving Mitigare. *See* JA51.

The district court first rejected as "entirely unsupported" Takeda's assertion that the FDCA requires FDA to compel an applicant to submit a certification if "*FDA* relies on other drug studies or data" when evaluating an application. JA54-55. The relevant provision "expressly applies only to the Section 505(b)(2) applicant, and pertains only to what application materials such sponsor is required to submit," the court explained. JA56-57. In any event, the court reasoned, even if Takeda's proposed reading of the statute were accepted, "the record here does not demonstrate FDA 'reliance' on Colcrys in its approval of Mitigare in the relevant sense." JA63. "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." JA65. Takeda's theory that FDA policy required West-Ward to rely on Colcrys similarly lacked merit: "Put bluntly," the court explained, Takeda's "argument hinges on the existence of an FDA drug reference policy that does not exist." JA67.

The court also rejected the claims that the FDCA or FDA regulations or policy required West-Ward to file a certification to Colcrys. JA67-85. Contrary to Elliott's arguments, the court concluded, the FDCA "is clear" that an applicant "need only certify to the product patents or the method-of-use patents that are associated" with "the drug *product* on whose investigations the 505(b)(2) applicant relied." JA75. The court identified "abundant" "textual support for this conclusion," explained that "the

overall structure of the statute" "only reinforced" "the plain meaning," and discussed how "the fundamental purpose of the Hatch-Waxman Amendments themselves confirms" the error of Elliott's view. JA76-85. The court dismissed Elliott's argument about "language in an FDA regulation that is nearly identical to the disputed statutory provision" as "entirely circular." JA84-85 n.25.

Finally, the court rejected Takeda's challenge to FDA's approval of Mitigare's labeling. JA85-95. Takeda argued that FDA had abandoned "specific labeling requirements" that FDA itself had established for all single-ingredient colchicine products; after carefully reviewing the record, the court ruled that "FDA did no such thing." JA86. "In any event," the court continued, it would defer to FDA's expert conclusions about what statements Mitigare's label should contain. JA92-93.

SUMMARY OF ARGUMENT

The district court correctly ruled that FDA acted lawfully by approving Mitigare. To start, FDA's decision to approve Mitigare without requiring West-Ward to file a certification to Colcrys's patents is consistent with the FDCA and FDA regulations and policy. As the district court explained, "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)." JA75. West-Ward's 505(b)(2) application did not rely on investigations of Colcrys. Instead, West-Ward's

application (like Mutual's application for Colcrys) relied on historical evidence and published literature about colchicine, as well as new studies that West-Ward conducted to support any proposed dose modification recommendations for Mitigare.

Takeda and Elliott nevertheless contend that FDA should have required West-Ward to file a certification to Colcrys's patents, although neither appellant supports the other's theories. Takeda asserts that the FDCA and FDA's own policy required West-Ward to file a certification to Colcrys's patents because FDA supposedly relied on investigations of Colcrys in order to approve Mitigare. But as the district court observed, the FDCA expressly links the certification requirement to the investigations "relied upon *by the applicant* for approval of the application." 21 U.S.C. § 355(b)(2) (emphasis added). Moreover, the record demonstrates that FDA relied on studies conducted by West-Ward as the basis for approving West-Ward's application, not on FDA's finding of the safety and effectiveness of Colcrys or studies in Mutual's application. Thus, Takeda's argument fails both legally and factually.

For its part, Elliott argues that the FDCA and FDA regulations required West-Ward to file a certification to Colcrys because Colcrys is protected by patents claiming uses of colchicine, and Mitigare contains colchicine. But accepting Elliott's arguments would require this Court to rewrite FDCA's certification provision and detach the provision from the section where Congress placed it, which "mandates reliance upon another drug's investigations as a non-negotiable prerequisite to any additional action on the part of the applicant." JA80. FDA regulations only confirm the essential

connection between an applicant's reliance and an applicant's certification obligations; the district court correctly observed that Elliott's contrary claim is both "entirely circular" and "mistaken." JA84-85 n.25.

The district court also correctly upheld FDA's choice of language for Mitigare's label. Takeda claims that prior statements by FDA establish sweeping labeling requirements for colchicine drug products that FDA must mechanically apply to Mitigare. But as the district court explained, none of the statements that Takeda cites purports to enshrine any such policy. In any event, as the record shows, Mitigare's label reflects FDA's expert assessment of the evidence, and FDA adequately explained the choices it made.

STANDARD OF REVIEW

This Court reviews FDA's decision under the familiar standards of the Administrative Procedure Act. "Accordingly," the Court "must uphold" FDA's decision "unless it is 'arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.'" *Mylan Laboratories, Inc. v. Thompson*, 389 F.3d 1272, 1279 (D.C. Cir. 2004) (quoting 5 U.S.C. § 706(2)). "In conducting this review," a court "show[s] considerable deference, especially where the agency's decision rests on an evaluation of complex scientific data within the agency's technical expertise." *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997); *see also Baltimore Gas & Electric Co. v. NRDC*, 462 U.S. 87, 103 (1983) ("When examining this kind of scientific

determination, as opposed to simple findings of fact, a reviewing court must generally be at its most deferential.").

An agency's interpretations of its authorizing statute and the agency's own regulations are also entitled to deference. That principle applies with special force here. As this Court has observed, "[t]here is no denying the complexity of the statutory regime under which the FDA operates, the FDA's expertise or the careful craft" of the agency in "reconcil[ing] the various * * * provisions" that Congress entrusted FDA to administer. *Mylan Laboratories, Inc.*, 389 F.3d at 1280.

ARGUMENT

THE DISTRICT COURT CORRECTLY UPHELD FDA'S DECISION TO APPROVE MITIGARE

A. FDA's Decision to Approve Mitigare Without Requiring West-Ward to File a Patent Certification to Colcrys Is Consistent with the FDCA and FDA Regulations and Policy

Takeda and Elliott assert that FDA acted unlawfully by approving Mitigare without requiring West-Ward to file a Paragraph IV certification to the use patents listed with FDA for Colcrys. The appellants first argue that the FDCA and FDA's own policy (according to Takeda) or the FDCA and FDA regulations (according to Elliott) required West-Ward to file a certification to Colcrys. Takeda further urges that the FDCA and FDA's own policy required West-Ward to file a Paragraph IV certification to Colcrys because, in Takeda's view, FDA relied on Colcrys to approve Mitigare. The district court correctly rejected all of these theories.

1. As the district court correctly reasoned, a 505(b)(2) applicant must certify to patents associated with "the drug product on whose investigations the 505(b)(2) applicant relies." JA75. Applicants seeking approval of "any drug" must submit "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." 21 U.S.C. § 355(b)(1)(A). An applicant must file "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 * * * and for which information is required to be filed" under the provision requiring an applicant to submit investigation reports in the first instance. *Id.* § 355(b)(2)(A); *see also id.* § 355(b)(1)(A) (requiring that an applicant "shall submit * * * full reports of investigations").

As FDA has explained in the past, the FDCA "explicitly links the *drug* relied on for approval to the *drug* for which patent certifications must be made." JA645. The statute "requires certifications to patents listed for *the drug product relied on for approval*." JA646. "Patent certification obligations thus 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." JA646-647. Consistent with FDA's understanding, the FDCA "lists the patents for which certifications are required *in a single sentence*—without break or numerical delineation." JA77. This repetition indicates that the patents to which the certification provision refers "are

generally of the same type and bear some relationship to one another, *i.e.*, both relate to" the drug on which the 505(b)(2) applicant chose to rely. *Ibid.*

The statute's structure buttresses its plain meaning. JA80. "The entire Section 505(b)(2) process" contemplates that applications may depend on FDA's findings of the safety and effectiveness of other drugs. JA80. The certification provision is part of a section that requires "reliance upon another drug's investigations as a non-negotiable prerequisite" to any obligation by the applicant. *Ibid.*; *see* 21 U.S.C. § 355(b)(2). An applicant's obligation to file a certification is triggered by the applicant's choice to include in an application "investigations * * * relied upon by the applicant for approval of the application" that "were not conducted by or for the applicant" and that "the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." 21 U.S.C. § 355(b)(2). An application "shall also include" a certification only if "[a]n application" contains such "investigations" and the applicant has "relied upon" those investigations. *Ibid.*

FDA's view also makes sense in light of the entire Hatch-Waxman scheme. "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)." JA81. FDA has explained that "[t]o divorce patent certification obligations from reliance and require" an applicant "to certify to patents on additional drug products * * * would upset the delicate balance struck by the

Hatch-Waxman Amendments," JA650, delivering an unjustified windfall to patent owners. As the district court observed, "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." JA82.

Finally, as FDA has also pointed out, requiring certifications only for patents associated with the drug product on which an applicant chooses to rely "treats ANDAs and 505(b)(2) applications comparably." JA647. "[S]uch treatment is a guiding principle for Hatch-Waxman interpretation that reflects the parallel structure and logic of the patent certification provisions." *Ibid.*; *see also* JA647 n.9 (citing prior consistent statements by FDA). "Just as ANDAs need only certify to patents on the listed drugs they reference and on which they rely for approval (and not to patents on other products in the product lines * * *) so too, are the 505(b)(2) applicant's patent certification obligations correlated to patents on the listed drug or drugs relied on for approval." JA647. In this way too, FDA's interpretation preserves Congress's goals.

2. a. Takeda nevertheless urges (in an argument that Elliott declines to join), that FDA should have required West-Ward to file a Paragraph IV certification about patents listed for Colcrys because, in Takeda's view, FDA "needed Colcrys data to approve the application" for Mitigare. Br. 17-18. As Takeda all but admits, this argument is wholly untethered from the text of the FDCA. Br. 16-17 ("agree[ing]" that an applicant's certification requirement "is straightforward" when an applicant

relies on "another drug's safety data" and pointing out that no statutory text addresses "when *FDA* relies on" another drug's safety data "to approve the application"). And contrary to Takeda's claim (Br. 17), grafting such a requirement onto the FDCA is not "[t]he only logical answer."

As the district court pointed out, the patent certification requirement "expressly applies only to the Section 505(b)(2) applicant, and pertains only to what application materials such sponsor is required to submit." JA56-57. The statute requires applicants to submit certifications if "the investigations * * * relied upon *by the applicant* for approval of the application were not conducted by or for the applicant" and "the applicant has not obtained a right of reference or use." 21 U.S.C. § 355(b)(2) (emphasis added). The certification must include "the opinion of the applicant" and facts "to the best of his knowledge." *Id.* § 355(b)(2)(A). "[T]he applicant" must notify patent holders within a set time after "the Secretary informs the applicant that the application has been filed" or, "if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement." *Id.* § 355(b)(3)(A)-(B). The notice must "include a detailed statement of the factual and legal basis of the opinion of the applicant" regarding the patent. *Id.* § 355(b)(3)(D)(ii).

Takeda proposes (Br. 17) that these provisions require FDA to force the applicant to follow the certification requirements if FDA "fills the gap" in an applicant's safety data. But that position has no basis in the statutory text, and it

would make a hash of the statute's operation. For example, it is far from clear how FDA would realize at the time that "the Secretary informs the applicant that the application has been filed" that any such gap exists; yet according to Takeda's theory, "the applicant" would still be required to "give notice as required under" the FDCA "not later than 20 days after the date of the postmark" on the Secretary's notification. 21 U.S.C. § 355(b)(3)(B)(i). Further, as Elliott rightly points out, "the Hatch-Waxman Act's quid pro quo" is between "applicants" and "patent holders." *See* Br. 29. As the district court explained, "there is no basis whatsoever" for the claim that Congress constructed the FDCA with the goal (of which no hint can be found in the statutory text) of making FDA a party to this bargain. JA60.

Rather than grapple with the anomalies that its reading would create, Takeda asserts (Br. 18-19) that a patchwork of excerpts from scattered sources demonstrates that "FDA itself previously held" Takeda's view. But Takeda's excerpts do not endorse Takeda's theory, much less suggest that FDA has "repeatedly adhered" to it. Takeda Br. 19. For example, Takeda cites (Br. 18) a Federal Register publication in which FDA stated that an investigation is "relied upon * * * for approval" if "the application could not be approved" without it. 54 Fed. Reg. 28,872, 28,891 (July 10, 1989). But as the very next sentences make clear, this statement merely explains when "an application is described by section 505(b)(2) of the" FDCA, rather than the provisions governing "a so-called 'full NDA'": "if the applicant has not conducted or

sponsored or obtained a right of reference to every safety or effectiveness investigation without which the drug could not be approved." *Ibid.*

Takeda also proffers (Br. 18-19) an excerpt from FDA's response to a prior citizen petition. But as the district court observed, "merely clarifies the limited scope of the applicant's patent certification obligation" and "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." JA61; *see* JA640-650 (FDA citizen petition response). And "in the course of pulling FDA's quotation out of context," Takeda ignores "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 relate[] solely to *the applicant's* reliance." JA61; *see, e.g.*, JA646-647 ("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."). In short, as the district court explained, there is "no basis for Takeda's contention" about FDA policy. JA62.

b. In any event, as the district court concluded, the record here "does not demonstrate FDA 'reliance' on Colcrys in its approval of Mitigare in the relevant sense," and hence the patent certification requirement would not be implicated even if this Court accepted Takeda's atextual reading of the FDCA. JA63-66.

As FDA explained, West-Ward's application provided adequate evidence of the safety and effectiveness of colchicine to treat gout flares prophylactically. *See* JA760-764; JA779-780; JA797-825. "[C]olchicine is a well-known drug and the efficacy and safety of colchicine in gout is well accepted." JA780; *see also* JA712 (observing as part of the "pertinent regulatory background or history" that "[a]pproval of Colcrys for prophylactic treatment of gout was based primarily on published literature and FDA's finding of safety and effectiveness for Col-Probenecid"). "[T]he clinical pharmacology data submitted" by West-Ward "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." JA780.

Takeda nonetheless insists (Br. 14, 21-24) that FDA used Mutual's "data to approve [West-Ward's] application," highlighting several excerpts from the record. But none of these excerpts supports Takeda's claim. Takeda first emphasizes (Br. 21-22) that FDA's Office of Prescription Drug Promotion "repeatedly compared the proposed Mitigare package insert to the approved Colcrys insert" and "raised concerns based on any discrepancies." But of course, the responsibility of that office is to review how drug information is communicated to patients and doctors. FDA, *The Office of Prescription Drug Promotion (OPDP)*, http://tinyurl.com/FDAopdp (last visited Oct. 15, 2015). [redacted]

[redacted]. This does not reveal that FDA relied on Mutual's studies "to show whether or not" Mitigare is safe and effective. 21 U.S.C. § 355(b)(1)(A). [redacted].

Takeda next asserts (Br. 22-23) that Mitigare's approved label "makes no sense without the Colcrys data." Takeda claims that the Mitigare label would not caution against combining colchicine with enzyme inhibitors but for Mutual's studies. But as FDA explained, "[c]olchicine's drug-drug interaction potential * * * has long been reported in the literature." JA712. [redacted].

The "widely-accepted specific recommendations for dose reduction in the setting of potential concomitant use of drugs with known interactions" had long been "avoidance when possible and caution when necessary, with vigilant monitoring of clinical signs of toxicity," even "[b]efore the approved labeling for Colcrys." JA895 (FDA memorandum); *see also* JA686 (same); JA699; JA701; JA705 (Mitigare label) (urging patients to avoid combining colchicine and enzyme inhibitors, and cautioning that "[i]f avoidance is not possible, reduced daily dose should be considered and the patient should be monitored closely for colchicine toxicity").

Finally, Takeda protests (Br. 22) that FDA "relied on Colcrys in analyzing the risk of drug-drug interactions," pointing to [redacted]. But as the district court correctly pointed out, "[t]he 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 Mutual's studies were required to approve West-Ward's application. JA65. FDA "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," JA66 n.17, to determine the proper regulatory approach. JA894. As the record shows, [redacted]

[redacted]. FDA approved Mitigare on the basis of West-Ward's evidence, not Mutual's studies. *See, e.g.*, JA779-780.

Unable to refute the record, Takeda resorts to alleging (Br. 17, 21, 24) that FDA "cloaked its action in conclusory statements" about the sufficiency of West-Ward's application, in order to hide that FDA had "worked with" West-Ward through "winks and nods" to evade Takeda's patents. Needless to say, this claim cannot be reconciled with the administrative record. FDA held West-Ward to the same patent certification requirements as any other applicant. Those requirements simply did not obligate West-Ward to make any certification to Colcrys.

c. Finally, Takeda contends (Br. 19-21) that by approving Mitigare, FDA abandoned a policy of requiring 505(b)(2) applicants to rely on the "most similar" previously approved drug and instead permitted West-Ward to "cherry-pick" an "outdated" reference "having little in common with the applicant drug." *See also* PhRMA Amicus Br. 27-28. But FDA's supposed policy is a creature of Takeda's creation. JA67 ("Put bluntly," the district court explained, this "argument hinges on the existence of an FDA drug reference policy that does not exist.").

As FDA has explained, the "applicant should determine" which previously approved drug or drugs are the "most appropriate" on which to rely. JA659. The reason is straightforward—"there is a direct correlation" between the previously approved drug on which the applicant elects to rely "and the applicant's burden of

proof." JA68; *see also* JA658. "An applicant choosing to rely on FDA's finding of safety and/or effectiveness for" a previously approved drug that is "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." JA658; *see also* JA648. But this choice is the applicant's to make. JA71 ("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."); JA658 (disclaiming any "statutory or regulatory requirement"). FDA's consistent and reasonable interpretation of the statute and the agency's own regulations is entitled to deference. *See, e.g.*, *Mylan Laboratories, Inc. v. Thompson*, 389 F.3d 1272, 1279-1280 (D.C. Cir. 2004); *Apotex, Inc. v. FDA*, No. 06-5060, 2007 WL 754768, at *1 (D.C. Cir. Feb. 23, 2007).

3. a. For its part, Elliott asserts (Br. 4, 24-27) that 21 U.S.C. § 355(b)(2)(A) requires West-Ward to file a certification to Colcrys because Colcrys is protected by patents claiming a use for colchicine, and colchicine is "the drug for which" West-Ward "was seeking approval." Elliott offers two arguments in support of this position, neither of which Takeda joins. Elliott first urges (Br. 24-25) that the references to "drug" in 21 U.S.C. § 355(b)(2)(A) must be read to encompass both a "drug product" and a "drug substance." Elliott next asserts (Br. 25-27) that the phrase "for which the applicant is seeking approval" should be understood to modify

the word "drug," rather than the word "use," on the theory any other reading would make 21 U.S.C. § 355(b)(2)(B) superfluous. As the district court explained, Elliott's interpretation stands at odds with the FDCA's text, structure, and purpose. JA77-84.

To start, Congress used the word "drug" when describing what patents require certification—"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); JA78. This repetition "strongly suggests" that Congress intended "drug" to have a consistent meaning. JA78; *see Brown v. Gardner*, 513 U.S. 115, 118 (1994) ("Since there is a presumption that a given term is used to mean the same thing throughout a statute," that presumption is "surely at its most vigorous when a term is repeated within a given sentence."). Consistent with the text, FDA has interpreted the word "drug" in 21 U.S.C. § 355(b)(2) "to refer to *drug product*, not *active ingredient*. Applications are submitted for drug products, not drug substances or active ingredients." JA645-646.

Further, the statute refers to "each patent which claims the drug for which such investigations were conducted or which claims a use for *such* drug." 21 U.S.C. § 355(b)(2)(A) (emphasis added). Congress's choice of the word "such" accentuates its intent to require certifications based on "the drug for which the relied-upon investigations were conducted." JA78. The phrase "such drug" plainly means "the drug for which such investigations were conducted," 21 U.S.C. § 355(b)(2)(A), "much like 'such investigations' plainly refers back to 'the investigations'" on which the

applicant elected to rely for approval of the application. JA79 (quoting 21 U.S.C. § 355(b)(2)(A)). Elliott's contrary reading "ignores 'such' entirely." JA79.[1]

Contrary to Elliott's claim (Br. 26-27), the link between the applicant's reliance and its certification obligation is only underscored by 21 U.S.C. § 355(b)(2)(B). If the applicant relies on investigations conducted for a previously approved drug covered by a method patent, and seeks approval for the same method of use as that previously approved product, a certification is required. 21 U.S.C. § 355(b)(2)(A). But if the previously approved drug's method patent "does not claim a use for which the applicant is seeking approval," only "a statement that the method of use patent does not claim such a use" is required. *Id.* § 355(b)(2)(B); *see also* JA80-81. The district court correctly reasoned that 21 U.S.C. § 355(b)(2)(B) "clearly works in conjunction with subsection (b)(2)(A), to address all method-of-use patents" for the drug on which the applicant relies. JA80-81.

[1] For the first time on appeal, Elliott urges in passing (Br. 24 & n.4) that "FDA's own regulations" support Elliott's view of the word "drug." This argument would fail even if Elliott had not forfeited it by failing to raise it below. The provision to which Elliott points, 21 C.F.R. § 314.50(i)(1)(i)(A), provides that an applicant must file "a certification with respect to each patent * * * that, in the opinion of the applicant and to the best of its knowledge, claims a drug (the drug product or drug substance that is a component of the drug product) on which investigations that are relied upon by the applicant for approval of its application were conducted or that claims an approved use for such drug." As this provision makes clear, an applicant's certification obligations depend entirely on the "investigations" on which the applicant chooses to rely. West-Ward's application relied for approval on "investigations" about Col-Probenecid, not Colcrys, as is reflected in FDA's finding of safety and effectiveness. *See supra* pp. 14-15.

Finally, Congress's purpose in enacting the Hatch-Waxman Amendments confirms the soundness of FDA's reading. JA81. As the district court observed, the Hatch-Waxman Amendments "balance two important and potentially conflicting objectives"—"protecting the innovator's work product" and "promoting efficient drug development" by other manufacturers. *Ibid.* On Elliott's reading, rather than a *quid pro quo* between new applicants and innovators, there would be "only a benefit for patent owners whose data is not being relied on by another manufacturer." JA82; *see also* JA82 n.23 (noting that "the very same paragraph" from the legislative history that Elliott quoted in district court—and quotes again on appeal, *see* Elliott Br. 27-28—"suggests that" that statute should "be read in precisely this fashion").[2]

b. Even if the statute were ambiguous in this regard, this Court should defer to FDA's "entirely reasonable" and "long-held" interpretation. JA84; *see also* JA85 ("[E]ven if a *Chevron* Step Two analysis was warranted, deference to FDA's reasonable

[2] Elliott also claims (Br. 29-30) that its interpretation is necessary to avoid the "perverse result" that patent holders will be unable to "litigate claims of patent infringement *before* the markets for their products are disrupted." *Cf.* Takeda Br. 20 (expressing concern that applicants will "avoid the pesky patent protections" of competitors). Of course, Takeda and Elliott have suffered no such harm—Takeda successfully prevented West-Ward from bringing its generic to market until after the Federal Circuit reviewed and rejected Takeda's patent claims. *See supra* pp. 16-18. Indeed, the district court's forthcoming ruling on West-Ward's motion to dismiss Takeda's amended patent infringement complaint may formally moot the certification issue here. *See* 21 U.S.C. § 355(c)(3)(C) ("[I]f before the expiration of" any stay of approval "the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on * * * the date on which the court enters judgment reflecting the decision.").

interpretation of the statute would be warranted as well."). As we have explained, FDA has consistently interpreted the statute to link an applicant's certification obligations to the previously approved drug or drugs on whose investigations the applicant chooses to rely. *See supra* pp. 24-26, 29, 35.

Elliott (in an argument that Takeda also declines to join) nevertheless asserts that FDA's long-standing view is inconsistent with an FDA regulation on the content and format of new drug applications. Br. 16-21. That regulation requires a certification "to each patent * * * that, in the opinion of the applicant and to the best of its knowledge, claims a drug * * * on which investigations that are relied upon by the applicant for approval of its application were conducted or that claims an approved use for such drug." 21 C.F.R. § 314.50(i)(1)(i). Recognizing that an applicant may rely on a previously approved product without seeking approval to market its product for all the same uses, the regulation also instructs that "[i]f the labeling of the drug product for which the applicant is seeking approval includes an indication that, according to the patent information submitted" by the applicant to FDA, "is claimed by a use patent, the applicant shall submit an *applicable* certification under paragraph (i)(1)(i) of this section." *Id.* § 314.50(i)(1)(iii)(B) (emphasis added). If "the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent," the applicant must include "a statement explaining that the method of use patent does not claim any of the proposed indications" of the applicant's product. *Id.* § 314.50(i)(1)(iii)(A).

Elliott argues that the word "applicable" must mean that "where the applicant's label contains an indication that is claimed in an existing method-of-use patent, the applicant must select *which* of the 'circumstances' enumerated in paragraph (i)(1)(i) applies," or else paragraph (1)(1)(iii)(B) would be superfluous. Elliott Br. 18-20. But as FDA has explained, this regulation serves to "reinforce" the "relationship between reliance and certification," JA646, not to sever the connection. Paragraph (i)(1)(i) by its terms applies only to "such patent[s]" that claim "a drug * * * on which investigations that are *relied upon by the applicant* for approval of its application were conducted or that claim[] an approved use for such drug." 21 C.F.R. § 314.50(i)(1)(i)(A) (emphasis added). It is for "such patent[s]," not any or all method-of-use patents, that a certification is required. *See ibid.* As the district court observed, Elliott's argument is both "entirely circular" and "mistaken." JA84-85 n.25.

B. FDA's Decision to Approve Mitigare's Labeling Is Consistent with FDA's Prior Statements

Takeda also contends (Br. 25-33) that FDA's approval of Mitigare should be rescinded because Mitigare's labeling does not contain statements that, according to Takeda, FDA had previously deemed "necessary for all single-ingredient oral colchicine products." As the district court observed, these arguments are doubly flawed. JA85-93. To start, none of the FDA statements cited by Takeda purports to establish agency policy for all future single-ingredient oral colchicine products under any circumstances. Moreover, as the record shows, FDA appropriately based its

choices about Mitigare's labeling on all relevant considerations, including the most recent scientific information and the indication for which Mitigare is approved.

1. Takeda first attacks the Mitigare label's statements about drug-drug interactions. Br. 25-28. Mitigare's label explains that "[c]olchicine can be administered with" certain enzyme inhibitors—the inhibitors tested in the West-Ward studies—"at the tested doses without a need for dose adjustments. However, these results should not be extrapolated to other co-administered drugs." JA701. The label further warns that "the drug-drug interaction potential of colchicine" with enzyme inhibitors "cannot be ruled out completely." JA705. Mitigare's label recommends that patients avoid combining colchicine and enzyme inhibitors other than the inhibitors tested in the West-Ward studies, and warns that "[i]f avoidance is not possible, reduced daily dose should be considered and the patient should be monitored closely for colchicine toxicity." JA699. The label also emphasizes the particular risk of combining colchicine with the enzyme inhibitor clarithromycin. JA698; JA699; JA700; JA701; JA705.

Takeda contends (Br. 26-27) that Mitigare's label cannot be reconciled with prior FDA "admonition[s] about the need for clear dose adjustments." But as the district court explained, "it cannot reasonably be asserted" that the prior FDA statements on which Takeda relies established a blanket policy for "the labels of all future" products. JA86-87. FDA has consistently maintained that labels must include "*appropriate* dosing and drug interaction information," meaning "*adequate* information

on drug-drug interactions" and "*relevant* dose adjustments needed to prevent unnecessary toxicity." *See* Takeda Br. 26 (quoting FDA statements) (emphases added). And as the district court correctly concluded, the record here shows that FDA was well aware of its prior statements, *e.g.*, JA777; JA895-899; JA911, and conducted "precisely the kind of individualized assessment of Mitigare's label" that FDA had "said would be required." JA88.

Mutual's studies suggested that enzyme inhibitors as a class create a risk of drug-drug interactions when used with colchicine products; West-Ward's subsequent studies suggested a more nuanced and less categorical relationship. FDA acted both permissibly and wisely in considering West-Ward's labeling in light of this information. FDA reasoned that [redacted]

FDA thus "engaged in an extensive analysis" of dose adjustments to determine "what dose instructions would adequately inform patients taking [enzyme] inhibitors how to use [Mitigare] safely." JA87-88. [redacted]

[redacted].

Ultimately, after considering a variety of options, FDA concluded that "a less prescriptive approach to drug interaction[] * * * treatment recommendations"—meaning a more general label warning—was "warranted." JA765-766; *see also* [redacted]. "[T]he most conservative approach would be for a prescriber to avoid" simultaneous use of certain enzyme inhibitors with colchicine or to combine the drugs "with caution, consideration of dose reduction, and close patient monitoring." JA765-766. Mitigare's FDA-approved label reflects this judgment. JA781 ("Because of" the agency's analysis of the evidence, "a less prescriptive approach * * * will be reflected in the label.").

Takeda does not seriously quarrel with FDA's explanation. Rather, Takeda faults FDA for failing to order West-Ward to include modified dosages for the specific enzyme inhibitors that Mutual studied, asserting that FDA "never explained why specific dose modifications were unwarranted for the drugs used in *Mutual's* studies." Br. 27-28. But as FDA pointed out, [redacted].[3]

FDA's judgment is entitled to deference. As the district court explained, "even if" courts "had the expertise to reevaluate" FDA's decision, they "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." JA94; *see also American Wildlands v. Kempthorne*, 530 F.3d 991, 1000 (D.C. Cir. 2008) ("The rationale for deference is

[3] [redacted].

particularly strong when the [agency] is evaluating scientific data within its technical expertise."). Here, FDA carefully evaluated the evidence and reached a considered judgment about how Mitigare's label should address the risk of drug interactions. Takeda identifies nothing in the record that casts doubt on this explanation.

2. Finally, Takeda challenges the Mitigare label's statement about acute gout flares. Br. 29-32. Mitigare's label includes among the "[l]imitations of use" of Mitigare that "[t]he safety and effectiveness" of Mitigare "for acute treatment of gout flares during prophylaxis has not been studied." JA625. The label also states that the maximum dose for patients taking Mitigare is 1.2 mg daily. *Ibid.* The recommended dose of Colcrys to treat acute gout flares is 1.8 mg over one hour. Takeda Br. 29 (explaining that "[t]he approved Colcrys label applies the data from the AGREE trial by recommending a maximum dose of 1.8 mg over a one-hour period").

Repeating the formula of its argument about drug interactions, Takeda begins by asserting (Br. 29-33) that Mitigare's label cannot be reconciled with a prior FDA "rule." Takeda locates this rule in FDA's response to Mutual's citizen petition, in which FDA "consider[ed] whether omission of certain labeling information regarding treatment of acute gout flares would render a proposed '*duplicate*' of Colcrys less safe or effective than Colcrys for prophylaxis of gout flares." JA691 (emphasis added). FDA concluded that "the labeling for a single-ingredient colchicine product seeking approval for prophylaxis of gout flares should inform healthcare providers that the lower dose colchicine regimen evaluated in the AGREE trial is adequate to treat an

acute gout flare that may occur during chronic colchicine use." *Ibid.* The agency cited past cases involving ANDA applicants and FDA's response to a prior citizen petition by a different drug manufacturer, which requested that FDA decline to approve ANDAs that omit certain information. JA691 nn. 72 & 75.

To start, contrary to Takeda's claim (Br. 29), this statement does not impose "a general requirement" that "indisputably includes Mitigare." As we explained above, because Mitigare is a capsule, not a tablet, Mitigare is not a duplicate of Colcrys and was not approved through the ANDA process. *See supra* p. 13. Far from representing "clear precedent" of "obvious relevance," Takeda Br. 31, 33, the statements in FDA's citizen petition response do not apply to Mitigare.

Regardless, as the district court explained, "the record clearly reflects the agency's well-reasoned and well-supported rationale" for approving Mitigare's label. JA90. Mitigare's label reflects "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." JA92-93. In an abundance of caution, FDA also deemed it wise for Mitigare's label "to note that Mitigare should not be used" for treatment of acute gout flares, because this use "has not been studied." JA773. Mitigare's label thus states under "[l]imitations of use" that Mitigare's "safety and effectiveness * * * for acute treatment of gout flares during prophylaxis has not been studied." JA625. FDA expected that this statement would dissuade healthcare

providers who "may be considering use of additional Mitigare for treatment of an acute gout flare in a patient receiving Mitigare for prophylaxis." JA773; *see also* [redacted].[4]

Here again, Takeda does not seriously dispute FDA's explanation; Takeda instead second-guesses FDA's expert choices. Takeda asserts (Br. 31-32) that the language FDA chose for Mitigare's label is too "ambiguous" and "bland[]." But as we explained above, FDA's determinations on such questions are "entitled to the highest degree of deference." JA94. As the district court concluded, "[t]he record demonstrates that FDA employed its scientific expertise to reach * * * reasoned conclusions about Mitigare's label, and the agency showed its work." JA93. "Takeda has not established that the APA requires anything more." *Ibid.*

[4] Consistent with Mitigare's label, its medication guide warns patients that "[i]t is not known if" Mitigare "is safe and effective for the treatment of" acute gout flares. JA635. The guide instructs patients that "[i]f you have a gout flare while taking" Mitigare, "tell your healthcare provider." JA636 ("How should I take Mitigare?").

CONCLUSION

For the foregoing reasons, the judgment of the district court should be affirmed.

Respectfully submitted,

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OCTOBER 2015

CERTIFICATE OF COMPLIANCE WITH FEDERAL RULE OF APPELLATE PROCEDURE 32(A)

I hereby certify that the sealed version of the government's brief complies with the type-volume limitation set forth in this Court's order of July 1, 2015, because it contains 11,507 words, excluding the parts of the brief exempted under Rule 32(a)(7)(B)(iii) and D.C. Circuit Rule 32(a)(1), according to the count of Microsoft Word. The foregoing public version of the government's brief is identical in content to the sealed version except that sealed material has been redacted.

I further certify that this brief complies with the requirements of Fed. R. App. P. 32(a)(5) and (6) because it has been prepared in 14-point Garamond, a proportionally spaced font.

/s/ Sonia K. McNeil
SONIA K. MCNEIL

CERTIFICATE OF SERVICE

I hereby certify that on October 16, 2015, I electronically filed the foregoing brief with the Clerk of the Court for the United States Court of Appeals for the District of Columbia Circuit by using the appellate CM/ECF system. I further certify that I will cause eight paper copies of this brief to be filed with the Court within three business days.

The participants in the case are registered CM/ECF users and service will be accomplished by the appellate CM/ECF system.

/s/ Sonia K. McNeil
SONIA K. MCNEIL

ADDENDUM

TABLE OF CONTENTS

Page(s)

21 U.S.C. § 355—New drugs.

(a) Necessity of effective approval of application.

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)

(b) Filing application; contents.

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (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. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

(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; and

(B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3) Notice of opinion that patent is invalid or will not be infringed

(A) Agreement to give notice

An applicant that makes a certification described in paragraph (2)(A)(iv) shall include in the application a statement that the applicant will give notice as required by this paragraph.

(B) Timing of notice

An applicant that makes a certification described in paragraph (2)(A)(iv) shall give notice as required under this paragraph—

(i) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or

(ii) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(C) Recipients of notice

An applicant required under this paragraph to give notice shall give notice to—

(i) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(ii) the holder of the approved application under this subsection for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(D) Contents of notice

A notice required under this paragraph shall—

(i) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(ii) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

* * *

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order.

(1) Within one hundred and eighty days after the filing of an application under subsection (b) of this section, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(A) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) of this section applies, or

(B) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(2) If the patent information described in subsection (b) of this section could not be filed with the submission of an application under subsection (b) of this section because the application was filed before the patent information was required under subsection (b) of this section or a patent was issued after the application was approved under such subsection, the holder of an approved application shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If the holder of an approved application could not file patent information under subsection (b) of this section because it was not required at the time the application was approved, the holder shall file such information under this subsection not later than thirty days after September 24, 1984, and if the holder of an approved application could not file patent information under subsection (b) of this section because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the Secretary shall publish it.

(3) The approval of an application filed under subsection (b) of this section which contains a certification required by paragraph (2) of such subsection shall be made effective on the last applicable date determined by applying the following to each certification made under subsection (b)(2)(A) of this section:

(A) If the applicant only made a certification described in clause (i) or (ii) of subsection (b)(2)(A) of this section or in both such clauses, the approval may be made effective immediately.

(B) If the applicant made a certification described in clause (iii) of subsection (b)(2)(A) of this section, the approval may be made effective on the date certified under clause (iii).

(C) If the applicant made a certification described in clause (iv) of subsection (b)(2)(A) of this section, the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in subsection (b)(3) of this section is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under paragraph (2) or subsection (b)(1) of this section before the date on which the application (excluding an amendment or supplement to the application) was submitted. If such an action is brought before the expiration of such days, the approval may be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under subsection (b)(3) of this section or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that—

(i) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on—

(I) the date on which the court enters judgment reflecting the decision; or

(II) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(ii) if before the expiration of such period the district court decides that the patent has been infringed—

(I) if the judgment of the district court is appealed, the approval shall be made effective on—

(aa) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(bb) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(II) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271(e)(4)(A) of title 35;

(iii) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in clause (i); or

(iv) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in clause (ii).

In such an action, each of the parties shall reasonably cooperate in expediting the action.

* * * *

21 C.F.R. § 314.50—Content and format of an application.

Applications and supplements to approved applications are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. Three copies of the application are required: An archival copy, a review copy, and a field copy. An application for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling, including, if applicable, any Medication Guide required under part 208 of this chapter. Other applications will generally contain only some of those items, and information will be limited to that needed to support the particular submission. These include an application of the type described in section 505(b)(2) of the act, an amendment, and a supplement. The application is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source. FDA will maintain guidance documents on the format and content of applications to assist applicants in their preparation.

* * *

(i) Patent certification—

(1) Contents. A 505(b)(2) application is required to contain the following:

(i) Patents claiming drug, drug product, or method of use.

(A) Except as provided in paragraph (i)(2) of this section, a certification with respect to each patent issued by the United States Patent and Trademark Office that, in the opinion of the applicant and to the best of its knowledge, claims a drug (the drug product or drug substance that is a component of the drug product) on which investigations that are relied upon by the applicant for approval of its application were conducted or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the act and § 314.53. For each such patent, the applicant shall provide the patent number and certify, in its opinion and to the best of its knowledge, one of the following circumstances:

(1) That the patent information has not been submitted to FDA. The applicant shall entitle such a certification "Paragraph I Certification";

(2) That the patent has expired. The applicant shall entitle such a certification "Paragraph II Certification";

(3) The date on which the patent will expire. The applicant shall entitle such a certification "Paragraph III Certification"; or

(4) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. The applicant shall entitle such a certification "Paragraph IV Certification". This certification shall be submitted in the following form: I, (name of applicant), certify that Patent No. _____ (is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product) for which this application is submitted.

The certification shall be accompanied by a statement that the applicant will comply with the requirements under § 314.52(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent and with the requirements under § 314.52(c) with respect to the content of the notice.

(B) If the drug on which investigations that are relied upon by the applicant were conducted is itself a licensed generic drug of a patented drug first approved under section 505(b) of the act, the appropriate patent certification under this section with respect to each patent that claims the first-approved patented drug or that claims an approved use for such a drug.

(ii) No relevant patents. If, in the opinion of the applicant and to the best of its knowledge, there are no patents described in paragraph (i)(1)(i) of this section, a certification in the following form:

In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the drug or drugs on which investigations that are relied

upon in this application were conducted or that claim a use of such drug or drugs.

(iii) Method of use patent.

(A) If information that is submitted under section 505(b) or (c) of the act and § 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, a statement explaining that the method of use patent does not claim any of the proposed indications.

(B) If the labeling of the drug product for which the applicant is seeking approval includes an indication that, according to the patent information submitted under section 505(b) or (c) of the act and § 314.53 or in the opinion of the applicant, is claimed by a use patent, the applicant shall submit an applicable certification under paragraph (i)(1)(i) of this section.

* * * *