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ORAL ARGUMENT NOT YET SCHEDULED

No. 15-5021 (consolidated with No. 15-5022)

IN THE

United States Court of Appeals for the District of Columbia Circuit

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TAKEDA PHARMACEUTICALS U.S.A., INC.,

Plaintiff-Appellant,

v.

SYLVIA MATHEWS BURWELL, IN HER OFFICIAL CAPACITY AS SECRETARY, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, *ET AL.*,

Defendants-Appellees,

and

HIKMA PHARMACEUTICALS PLC, *ET AL.*,

Intervenor-Appellees.

On Appeal from the
United States District Court for the District of Columbia
Case No. 1:14-cv-1668 (Hon. Ketanji Brown Jackson)

OPENING BRIEF FOR APPELLANT TAKEDA PHARMACEUTICALS U.S.A., INC.

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August 17, 2015

CERTIFICATE OF PARTIES, RULINGS, AND RELATED CASES

Pursuant to Circuit Rule 28.1(a)(1), the undersigned counsel for Appellant Takeda Pharmaceuticals U.S.A., Inc. submits this Certificate of Parties, Rulings, and Related Cases.

(A) Parties and Amici.

Plaintiffs in the court below and Appellants in this Court are Takeda Pharmaceuticals U.S.A., Inc.; Elliott Associates, L.P.; Elliott International, L.P.; and Knollwood Investments, L.P. Pursuant to Rule 26.1 of the Federal Rules of Appellate Procedure and Circuit Rule 26.1, the undersigned counsel further submits that:

Appellant Takeda Pharmaceuticals U.S.A., Inc. is a pharmaceutical company that sells a patented colchicine product, Colcrys®. Takeda Pharmaceuticals U.S.A, Inc. is a wholly owned subsidiary of Takeda America Holdings, Inc., which is in turn a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. Takeda Pharmaceutical Company Limited is a publicly traded company listed on the Tokyo Stock Exchange.

Defendants in the court below and Appellees in this Court are Sylvia Mathews Burwell, in her official capacity as Secretary, U.S. Department of Health and Human Services; and Margaret A. Hamburg, in her official capacity as Commissioner of Food and Drugs, Food and Drug Administration.

Intervenor-Defendants in the court below and Appellees in this Court are Hikma Pharmaceuticals PLC and West-Ward Pharmaceutical Corp.

Amicus in this court is the Pharmaceutical Research and Manufacturers of America.

(B) Rulings Under Review. Appellant seeks review of the District Court's (Judge Ketanji Brown Jackson) January 12, 2015 Memorandum Opinion (Docket 74) and accompanying January 15, 2015 Order (Docket 77) denying Takeda's motion for summary judgment and dismissing Takeda's complaint. The Order is reproduced in the Joint Appendix (JA) at JA98, and the Memorandum Opinion is reproduced at JA18-97 and is available at 2015 WL 252806. The ruling under review pertains to FDA's approval of an application submitted by Hikma Pharmaceuticals PLC under Section 505(b)(2) of the Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(b)(2), for permission to market Mitigare colchicine capsules for prophylaxis of gout flares. Excerpts of the administrative record relating to FDA's approval decision are reproduced at JA668-960.

(C) Related Cases. The case on review has not been previously before this Court or any other court. There is one case involving the same parties and some related issues (pertaining to Takeda's patents) that was decided by the United States Court of Appeals for the Federal Circuit: *Takeda Pharmaceuticals U.S.A.,*

Inc. v. West-Ward Pharmaceutical Corp., Nos. 2015-1139, 2015-1142. To the best of counsel's knowledge, there are no other potentially related cases.

/s/ Catherine E. Stetson
Catherine E. Stetson

Counsel for Appellant Takeda Pharmaceuticals U.S.A., Inc.

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GLOSSARY

ANDA: Abbreviated New Drug Application

CYP3A4: Cytochrome P450 3A4

FDA: Food and Drug Administration

NDA: New Drug Application

P-gp: P-glycoprotein

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JURISDICTIONAL STATEMENT

This is an appeal from the District Court's January 12, 2015 Opinion and January 15, 2015 Order denying Takeda's motion for summary judgment and dismissing Takeda's complaint. Takeda filed a timely notice of appeal on January 20, 2015. ECF No. 82. This Court has jurisdiction pursuant to 28 U.S.C. § 1291.

INTRODUCTION

In 1984, after decades of trial and error, Congress created an ambitious new framework for the approval of prescription drugs. Often referred to as the Hatch-Waxman Amendments, the legislation was no small feat: Congress sought to encourage innovation and investment, promote competition and lower prices, and ensure the safety and effectiveness of prescription drugs.

Those goals required significant trade-offs, including a new approval process for certain drugs that *resembled* previously approved drugs but were not quite generic versions. For those drugs, the Hatch-Waxman Amendments provide that a manufacturer may rely on the Food and Drug Administration's prior approval of a similar drug—thus speeding the new drug to market. But any reliance triggers immediate notice to the patent-holder of the relied-upon drug—thus protecting innovators' intellectual property. *See* 21 U.S.C. § 355(b)(2).

In this case, FDA short-circuited that careful legislative scheme. It approved Hikma's application for an oral colchicine product (Mitigare) that is nearly identical to Takeda's oral colchicine product (Colcrys®). In doing so, FDA relied on Takeda's Colcrys data but allowed Hikma to formally list a different drug, thereby circumventing the statutory notification requirements that are a crucial component of the Hatch-Waxman Amendments. FDA also ignored its prior

precedents about colchicine labeling, which separately would have triggered the notification requirements.

In both respects, FDA's actions were arbitrary and capricious and contrary to law. The District Court's decision holding otherwise should be reversed.

ISSUES PRESENTED FOR REVIEW

1. Whether FDA's approval of Mitigare was unlawful or arbitrary and capricious because the application for Mitigare impermissibly failed to reference Colcrys and to make the appropriate patent certifications.

2. Whether FDA's approval of Mitigare was arbitrary and capricious because the approved label omits critical safety information that FDA had previously concluded was necessary for *all* single-ingredient colchicine products.

PERTINENT STATUTES & REGULATIONS

Pertinent statutes and regulations are reproduced in the Addendum.

STATEMENT OF FACTS

I. STATUTORY BACKGROUND

A. The New Drug Approval Process.

Under the Food, Drug, and Cosmetic Act, FDA must approve all prescription drugs before they can enter the marketplace. 21 U.S.C. § 355(a). There are three different paths to approval: (1) a full New Drug Application (NDA), (2) an Abbreviated New Drug Application (ANDA), and (3) an intermediate process known as a Section 505(b)(2) NDA.

The full NDA process requires the manufacturer of a brand-name, or "innovator," drug to submit detailed data demonstrating that the drug is safe and effective. *Id.* § 355(b)(1). At the other end of the spectrum, an ANDA applicant may obtain approval for a generic version of an innovator drug by demonstrating that the generic drug is equivalent to the innovator drug. *Id.* § 355(j)(2)(A). Option three, the Section 505(b)(2) NDA, is a hybrid approach. As its name indicates, a 505(b)(2) NDA is technically a type of NDA—meaning that an applicant must ultimately demonstrate that the proposed drug is safe and effective. *Id.* § 355(b)(2). Like an ANDA applicant, however, a 505(b)(2) applicant may rely on studies submitted to FDA by a third party in support of a previously approved drug. *Id.*

A Section 505(b)(2) NDA is often appropriate where a new drug differs from an innovator drug in limited ways. For example, if a new drug uses a different dosage form, strength, or administration route, a 505(b)(2) applicant may rely on the innovator drug's approval. But it must fill in the gap by demonstrating that the distinguishing characteristic of the new drug does not make it any less safe or effective.

B. The Hatch-Waxman Certification Requirement.

The ANDA and 505(b)(2) pathways expedite the approval process, bring competitor drugs to consumers, and reduce the need for duplicative scientific

research. Such benefits, though, capitalize on the earlier efforts—and substantial investments—of innovator companies. To protect those companies, and to preserve incentives for future innovation, Congress passed the Hatch-Waxman Amendments to the Food, Drug, and Cosmetic Act. In the legislation, "Congress sought to strike a balance between incentives, on the one hand, for innovation, and on the other, for quickly getting lower-cost generic drugs to market." *Teva Pharm. Indus. Ltd. v. Crawford*, 410 F.3d 51, 54 (D.C. Cir. 2005).

Under Hatch-Waxman, when a drug product is approved via an NDA (including a 505(b)(2) NDA), FDA records patent information about the drug in a publication commonly called "the *Orange Book*." If the drug is the first-approved product of its kind, FDA will designate the product as a "reference-listed drug" on which subsequent applicants may rely. *See* 21 C.F.R. § 314.3(b).

When a 505(b)(2) applicant later relies on a reference-listed drug, the applicant must include "certifications" to the patents listed in the *Orange Book* for that drug. 21 U.S.C. § 355(b)(2)(A). Specifically, the applicant must certify that (i) no such patents exist, (ii) any such patents have expired, (iii) the proposed drug will not be marketed before the patents expire, or (iv) any patents are invalid or will not be infringed by the proposed drug. *Id.* § 355(b)(2)(A)(i)-(iv). The last option, known as a "Paragraph IV" certification, triggers an additional obligation to notify the drug's manufacturer. *Id.* § 355(b)(3)(A). A Paragraph IV notice must

"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." *Id.* § 355(b)(3)(D).

A Paragraph IV notice is important; it allows the manufacturer of the referenced drug to litigate any patent claims promptly, *before* FDA approves the 505(b)(2) application and the new drug reaches the market. The statute encourages this early resolution of patent claims by treating the submission of a 505(b)(2) application as a technical act of patent infringement. *See* 35 U.S.C. § 271(e)(2). The manufacturer then has 45 days from receipt of the Paragraph IV notice to bring an infringement action against the 505(b)(2) applicant. 21 U.S.C. § 355(c)(3)(C). If it does so, FDA must stay its approval of the 505(b)(2) application for 30 months, or until specified events occur in the patent litigation. *Id.*

II. PROCEDURAL BACKGROUND

A. Colchicine.

Colchicine is a toxin derived from the *Colchicum Autumnale* plant. For centuries, it has been used to treat gout—a common metabolic disorder characterized by deposits of uric acid crystals that produce intense bouts of arthritis. *See* JA670-671. Colchicine has a "narrow therapeutic index," meaning that only a small range of doses provides therapeutic benefits without causing severe complications. 75 Fed. Reg. 60768, 60769 (Oct. 1, 2010). Given that

narrow therapeutic index, unapproved colchicine products have been linked to a number of serious adverse events over the last 50 years. *Id.* In 2008, FDA announced it would take enforcement action against unapproved colchicine products on the market. 73 Fed. Reg. 7565 (Feb. 8, 2008).

B. FDA Approves Colcrys.

In 2009, FDA approved Mutual's application for Colcrys, making Colcrys the first FDA-approved, single-ingredient oral colchicine product. JA672.[1] FDA approved Colcrys for the treatment of Familial Mediterranean Fever (a rare disease not at issue in this case) and for the treatment and prophylaxis of acute gout flares. JA672-673.

To obtain the gout approvals, Mutual conducted extensive research. In particular, it performed two sets of studies designed to evaluate colchicine toxicity and to reduce colchicine fatalities by (1) minimizing drug-drug interactions, and (2) analyzing the efficacy of a low-dose colchicine regimen.

Drug-Drug Interactions. Before Colcrys's approval, FDA data had identified 751 adverse events, including 169 deaths, associated with colchicine toxicity. JA674. More than half of the deaths not reported as overdoses were related to the concomitant use of colchicine and clarithromycin, a common antibiotic. *Id.* Mutual thus undertook eight studies to compare the effects of

[1] Takeda later acquired Mutual and its rights to Colcrys.

colchicine administered alone to colchicine administered with other drugs. The studied drugs included clarithromycin and other cytochrome P450 3A4 (CYP3A4) inhibitors, and P-glycoprotein (P-gp) inhibitors. JA146, 160-161. Mutual discovered that certain drugs significantly raise colchicine levels in the blood. For example, the co-administration of clarithromycin causes colchicine blood levels to increase by more than 200%. JA146. In light of those results, Mutual developed a new dosing regimen for the co-administration of Colcrys with other drugs. Mutual created several detailed tables that provide dose adjustments for colchicine when administered either with the specific drugs Mutual had studied or with other similar-acting drugs. Those tables are displayed on the Colcrys label. JA134-135.

In its clinical pharmacology review of Colcrys, FDA emphasized the significant results of these drug-drug interaction studies. *See* JA165. The agency even issued a Safety Alert to healthcare professionals, explaining the "important safety considerations" highlighted by Mutual's studies and referring physicians "to Colcrys' approved prescribing information for specific dosing recommendations and additional drug interaction information." JA126.

Low-Dose Regimen. Mutual also studied whether lower doses of colchicine could be effective in treating acute gout flares. It conducted a randomized, double-blind clinical trial known as the "AGREE trial." *See* JA689. The results were remarkable. Historically, doctors had recommended that patients suffering from

acute gout flares take 1.2 mg of colchicine followed by 0.6 mg every hour until the flare resolves or until gastrointestinal toxicity occurs—a regimen that could result in a total dose of 4.8 mg, and significant adverse side effects. JA127-128. The low-dose regimen Mutual tested, by contrast, consisted of 1.2 mg followed by 0.6 mg one hour later, for a total dose of 1.8 mg. JA128. Mutual surprisingly found that its low-dose regimen was *just as effective* for treating acute gout flares as the traditional regimen. *Id.* The low-dose regimen, moreover, resulted in a significantly reduced rate of gastrointestinal side effects: 26%, compared to 77% with the high-dose regimen. *Id.* And while ten patients on the high-dose regimen suffered severe adverse events, zero patients on the low-dose regimen did so. *Id.*

Given these results, the Colcrys label reflects the low-dose regimen. *See* JA130, 132. The label emphasizes that "[h]igher doses have not been found to be more effective" and that the "maximum recommended dose for treatment of gout flares is 1.8 mg." JA132. As with Mutual's drug-drug interaction studies, FDA's Safety Alert directs healthcare professionals to the Colcrys label for low-dose information, and recommends that practitioners "prescribe the FDA-approved Colcrys dose for the treatment of acute gout flares." JA126.

Because of its innovative work analyzing drug-drug interactions and developing the low-dose colchicine regimen, Mutual sought and received patents

for Colcrys. The *Orange Book* originally listed five Colcrys patents relating to methods of using colchicine, though more have been added since. JA675.

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

In the fall of 2010, Mutual learned that Hikma and its U.S. manufacturer, West-Ward Pharmaceutical Corp., had submitted an application to FDA for a 0.6 mg, single-ingredient oral colchicine tablet—a duplicate of Colcrys. When Mutual did not receive a Paragraph IV notice, it filed a Citizen Petition with FDA seeking clarification of its rights under Hatch-Waxman. As relevant here, Mutual requested that FDA:

- "Refrain 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";
- "Refrain 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
- "Require the labeling for any single ingredient oral colchicine product to include all information related to drug-drug interactions that is in the Colcrys labeling, including relevant dose adjustments needed to prevent unnecessary toxicity[.]"

JA176.

FDA granted the petition in large part. *First*, FDA confirmed that Hikma had inappropriately submitted a 505(b)(2) application for a duplicate version of

Colcrys. FDA therefore required Hikma to withdraw the application and resubmit it as an ANDA. JA679-683.

Second, FDA agreed that the information Mutual had developed about drug-drug interactions was critical to the safe labeling of colchicine products. It explained that Mutual's studies "provided new, quantitative information about the extent of changes in exposure that can occur with co-administration of certain drugs with colchicine." JA686. Because of that information, "the requirements for approval of a single-ingredient colchicine product have changed." JA683.

Third, FDA emphasized that the low-dose regimen developed in the AGREE trial was necessary to the safe labeling of *any* single-ingredient colchicine product seeking approval for prophylaxis of gout flares. JA670. It stated that the labeling for such products "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.*; *see also* JA691.

D. FDA Approves Mitigare.

Years passed. Mutual never received a Paragraph IV notice, suggesting that Hikma had declined FDA's invitation to resubmit its application as an ANDA.

Then, in September 2014, FDA approved a colchicine product manufactured by Hikma. The product, Mitigare, is a 0.6 mg, single-ingredient oral colchicine *capsule* indicated for prophylaxis of gout flares. JA695. Because Mitigare had

been reformulated as a *capsule* rather than a *tablet*, it was no longer an exact duplicate of Colcrys and did not have to travel the ANDA pathway; Hikma had (re)submitted it under Section 505(b)(2). But even under the 505(b)(2) pathway, the Mitigare application should have referenced Colcrys as a relied-upon drug. Hikma did not list Colcrys in its application, however. It cited an older combination drug, Col-Probenecid, instead. As a consequence, Takeda did not receive a Paragraph IV notice, thus losing the opportunity to initiate and litigate a patent suit during the statutorily mandated 30-month stay of FDA approval. And while Colcrys may not have appeared in the screen credits, it clearly played a starring role; [redacted].

The approved Mitigare label also omits the warnings derived from the two sets of Colcrys studies. With respect to drug-drug interactions, the Mitigare label ignores the specific Colcrys dose adjustments. The prescribing information cautions about drug-drug interactions only in general terms: "[C]oncomitant use of MITIGARE and inhibitors of CYP3A4 or P-glycoprotein should be avoided. . . . If avoidance is not possible, reduced daily dose should be considered and the patient should be monitored closely for colchicine toxicity." JA699. The same goes for the low-dose regimen, which is nowhere to be found on the Mitigare label. In its place is a vague disclaimer that the "safety and effectiveness of MITIGARE for acute treatment of gout flares during prophylaxis has not been studied." *Id.*

E. Takeda Files Suit.

In October 2014, Takeda filed a complaint challenging FDA's approval of Mitigare, along with a motion for a preliminary injunction. Takeda also initiated a patent infringement action. *See Takeda Pharms. U.S.A. v. West-Ward Pharm. Corp.*, No. 14-1268 (D. Del.). In this APA suit, the District Court converted Takeda's preliminary injunction motion into a summary judgment motion, denied summary judgment, and dismissed the complaint. The court held that FDA had not acted arbitrarily and capriciously in approving Mitigare under the 505(b)(2) pathway, notwithstanding Hikma's failure to reference Colcrys and the clear discrepancies between the Mitigare label and the Colcrys label. *See* JA22-23. Takeda appealed.

STANDARD OF REVIEW

A court must set aside agency action that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). "[E]ven pursuant to this deferential standard of review, an agency must articulate an explanation for its action." *Amerijet Int'l, Inc. v. Pistole*, 753 F.3d 1343, 1350 (D.C. Cir. 2014). Agency action is arbitrary and capricious if the agency departs from its own precedent without providing a reasoned explanation. *See Friedman v. Sebelius*, 686 F.3d 813, 828 (D.C. Cir. 2012).

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Because the District Court assessed FDA's actions under the APA, this Court reviews the agency action "directly, according no particular deference to the judgment of the District Court." *Holland v. Nat'l Mining Ass'n*, 309 F.3d 808, 814 (D.C. Cir. 2002).

SUMMARY OF ARGUMENT

In its haste to usher a Colcrys competitor to market, FDA violated the APA in at least two ways. *First*, FDA approved Hikma's 505(b)(2) application without requiring Hikma to reference Colcrys and to make the Paragraph IV certifications required by statute. Under Hatch-Waxman, a 505(b)(2) applicant must certify to patents for each previously approved drug "relied upon by the applicant for approval of the application." 21 U.S.C. § 355(b)(2). FDA emptied the statute of effect by permitting an applicant to certify *only* to those drugs expressly named in its application—even if FDA uses an unnamed drug's data to approve the application. That is inconsistent with the statutory text, with common sense, and with FDA's longstanding interpretation that an applicant must certify to any drugs without which "the application cannot be approved." JA834.

And it is clear that Colcrys was necessary to Mitigare's approval, despite Hikma's gerrymandering of its application to avoid mentioning Colcrys. [redacted]

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[redacted] The approved label for Mitigare also includes cautionary language consistent with the Colcrys data—but inconsistent with Hikma's own studies. JA699-701. Page after page of the administrative record belies FDA's conclusory assertion that Colcrys was unnecessary to the agency's decision to approve Mitigare.

Second, FDA acted arbitrarily and capriciously in approving Hikma's 505(b)(2) application without requiring the Mitigare label to include critical safety information it had previously deemed essential. After Mutual's groundbreaking studies, FDA determined that information about dose adjustments and a low-dose colchicine regimen was mandatory for all single-ingredient oral colchicine products' labels. JA670. The Mitigare label omits both types of information. FDA gave no reasoned explanation for allowing those omissions. [redacted] The agency gave an even weaker explanation for its inconsistency about the low-dose regimen. [redacted], but failed to acknowledge that the agency had previously rejected that very distinction. JA670, 691.

For any one of these reasons, FDA's decision to approve Hikma's 505(b)(2) application violated the APA. The District Court's decision should be reversed.

ARGUMENT

I. FDA IMPERMISSIBLY APPROVED HIKMA'S 505(b)(2) APPLICATION WITHOUT REQUIRING HIKMA TO REFERENCE COLCRYS.

The 505(b)(2) approval process involves several carefully calibrated tradeoffs. As FDA itself has acknowledged, "[t]his approach is intended to encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug, while protecting the patent and exclusivity rights for the approved drug." JA204.

Yet in this case, FDA helped Hikma evade important Hatch-Waxman obligations. Colcrys data was necessary to FDA's approval of Mitigare, so Hikma was required by statute to certify to the Colcrys patents in the *Orange Book*. It did not. FDA's decision to approve Hikma's 505(b)(2) application without those certifications was arbitrary and capricious and contrary to law.

A. A 505(b)(2) Applicant Must Reference Any Drug Necessary To FDA's Approval.

The Hatch-Waxman certification requirement is triggered whenever a previously approved drug is "relied upon by the applicant for approval of the application." 21 U.S.C. § 355(b)(2).

All parties agree that this statutory obligation is straightforward when an *applicant* references another drug's safety data in a 505(b)(2) application: The applicant must certify to patents for the listed drug. But what does the statute

require when *FDA* relies on that listed drug to approve the application? Or, to put it another way, what happens when an application has a gap, and FDA fills the gap with another drug's safety data? The only logical answer is that the applicant has still "relied upon" the other drug "for approval of the application"; after all, the application would not otherwise have been approved. The applicant must therefore certify to patents for the relied-upon drug, and FDA cannot approve the application until the applicant does so.

If FDA concludes that it cannot find that the proposed drug is safe and effective based only on the materials an applicant has submitted, it can reject the application. The applicant can then revise the application by conducting additional studies, or by identifying a previously approved drug and certifying to its patents. Here, however, FDA worked with Hikma to skip those steps. There was a yawning gap in Hikma's 505(b)(2) application; Hikma quite intentionally omitted any citation to Colcrys. But FDA did not reject Hikma's application outright; it filled the gap with the Colcrys data *itself*, then approved the application. Because FDA needed Colcrys data to approve the application, that data was "relied upon by the applicant for approval of the application," 21 U.S.C. § 355(b)(2)—no less than if Hikma had properly included it in the first place.

Any decision to the contrary would permit a flagrant end-run around Section 505(b)(2). An applicant could escape the Hatch-Waxman certification requirement

by submitting a barebones 505(b)(2) application and trusting FDA to fill in the blanks whenever the agency believed (for example) that a proposed drug was sufficiently important and time-sensitive to warrant that treatment. There is no indication in the statute that the agency has such power to waive the patent certification requirements as it sees fit.

FDA itself previously held this view of the statute, explaining that investigations "relied upon . . . for approval" means "any investigations *without which the application could not be approved*." 54 Fed. Reg. 28872, 28891 (July 10, 1989) (emphasis added); *see also* JA202 (explaining that the 502(b)(2) process "expressly permits *FDA* to rely, for approval of an NDA, on data not developed by the applicant") (emphasis added). FDA has accordingly instructed applicants to certify "to patents listed for drugs on whose finding of safety and effectiveness *FDA relies for approval*." JA649 (emphasis added); *see also* JA1049 (right of reference "permitted FDA to refer to the safety and effectiveness data in the Norvasc NDA during the Agency's review of the Lotrel NDA *and to rely on that information to approve* Lotrel") (emphasis added).

In fact, FDA's own standard 505(b)(2) Assessment Form adopts an appropriately nuanced view of reliance. The Form asks:

> Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the

> proposed drug product (*i.e. the application cannot be approved without this reliance*)?

JA834 (second emphasis added). Thus, until now, FDA repeatedly adhered to the rule that if *it* relies on another drug's safety data to approve an application, the applicant must certify to that drug's patents.

The District Court rejected this commonsense conclusion because it focused on FDA's *ability* to access data rather than the *consequence* of that access. In the court's view, the "linchpin" of Takeda's argument was "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." JA55 (emphasis added). But that is not what Takeda argued at all. Hatch-Waxman does not prohibit *FDA* from consulting third-party data. But it does require an *applicant* to reference another drug if FDA relies on that drug's safety and effectiveness to approve a 505(b)(2) application. If the applicant fails to reference that drug, the application is deficient. And FDA cannot approve the application until the deficiency is corrected.

To make matters worse, the District Court permitted FDA to walk away from its own previous policy governing which drugs a 505(b)(2) applicant must reference. FDA once required 505(b)(2) applicants to "choose the listed drug or drugs that are *most similar* to the drug for which approval is sought." JA648

(emphasis added). FDA later recast its "most similar" standard as a "most appropriate" standard, allowing an applicant to reference any listed drug that is "scientifically appropriate." JA659. But even the "most appropriate" standard is an objective one: FDA reviewers must determine whether "there is an approved drug product that is equivalent or very similar to the product proposed for approval that *should be referenced* as a listed drug." JA835 (emphasis added).

In this case, however, FDA jettisoned its "most appropriate" standard and deemed *any* listed drug appropriate, so long as a 505(b)(2) applicant provides some data to explain the difference between the proposed drug and the listed drug. FDA's unexplained departure means that the agency now imposes *no* objective criterion for choosing a listed drug.

The combination of FDA's failure to enforce its "most appropriate" standard and the District Court's free pass for FDA reliance creates a gaping loophole in Hatch-Waxman. Manufacturers like Hikma can now cherry-pick an outdated reference-listed drug having little in common with the applicant drug, to avoid the pesky patent protections of the obvious comparator. That is why—according to Hikma's own counsel—the Mitigare application referenced Col-Probenecid. *See* JA348 ("Certainly Hikma relied on Col-Probenecid instead of Colcrys to avoid patents. We're not going to dispute that."); [redacted]. Under the District Court's new regime, a 505(b)(2) applicant can omit a nearly identical listed

drug, trusting FDA to examine the more germane and recent data from that obvious-but-omitted drug—all without any consequences for the applicant. With that simple system of winks and nods, the applicant and FDA can circumvent Hatch-Waxman's certification requirement entirely.

B. FDA Relied On Colcrys Data To Approve Hikma's 505(b)(2) Application.

When pressed, FDA has accepted Takeda's commonsense reading of the statute. *See* JA338 (FDA's counsel: "if FDA had relied, FDA would have rejected this application because it wouldn't be complete"). But the agency contends that it did not actually rely on Colcrys data in reviewing and approving Hikma's application. *See* JA338-339.

The administrative record belies that contention. FDA extensively relied on proprietary Colcrys data; [redacted]. To be sure, not every mention of another drug necessarily equates to reliance. But the pervasiveness of the Colcrys data in FDA's analysis is a strong indication that Colcrys was key to Mitigare's approval. Several particular references underscore the point. [redacted]

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[redacted]

FDA also relied on Colcrys in analyzing the risk of drug-drug interactions:

[redacted]

Colcrys data was clearly a central consideration—if not *the* central consideration—in FDA's decisions whether to approve Mitigare and what the Mitigare label should say about drug-drug interactions. *See* JA935.

Even if the administrative record did not reveal the agency's heavy reliance on Colcrys, the finished product does; for Mitigare's approved label makes no sense without the Colcrys data. [redacted]

MATERIAL UNDER SEAL DELETED

[redacted] Yet the approved Mitigare label does not merely dispense with the Mutual warnings; it cautions against the co-administration of Mitigare and P-gp or CYP3A4 inhibitors—warnings consistent with *Mutual's* studies but not with Hikma's. *See* JA700-702. FDA's counsel conceded below that "if no drug interaction studies had ever been done that showed an impact, *you wouldn't see that sort of warning in the label*." JA261 (emphasis added). That is well put: If the Colcrys studies had not been performed, the Mitigare label would not look the way it does. The word to describe that is "reliance."

It is no response that FDA might have invoked studies other than Mutual's. Although prior literature suggested the possibility of drug-drug interactions, only Mutual's studies provided quantitative information to explain reports of adverse events. *See* JA674 (prior literature provided "some general information on drug-drug interactions with colchicine," but the "studies conducted by Mutual provided important data to inform FDA's dosage recommendations"); JA686 ("Before the approved labeling for Colcrys, there were no widely-accepted specific

recommendations for dose reduction"). The Mitigare label even includes a veiled reference to such quantitative information, noting that certain drugs cause "significant increases in systemic colchicine levels." JA699. On top of that, the Colcrys label was the first to address drug-drug interactions by suggesting precise dose reductions. The Mitigare label similarly calls for dose reductions—it simply does so without giving specific guidance to physicians. *See id.*

The District Court responded to this overwhelming evidence of reliance by pointing to FDA's occasional statements that Hikma's application was sufficient without the Colcrys data. JA65. But the mere fact that the agency cloaked its action in conclusory statements cannot be dispositive in this APA challenge. The administrative record reveals that FDA repeatedly turned to proprietary Colcrys data to assess and approve the Mitigare application. FDA cannot now wave its hands and prevent this Court from examining that record. If the agency need only claim that it did not rely on Colcrys data—notwithstanding an administrative record peppered with references to Colcrys, comparisons to Colcrys, and decisions based on Colcrys—then APA review would be meaningless. *See Amerijet Int'l*, 753 F.3d at 1350 (the "fundamental requirement of administrative law is that an agency set forth its reasons for decision").

II. FDA DEPARTED FROM AGENCY PRECEDENT IN APPROVING A MITIGARE LABEL LACKING CRITICAL SAFETY INFORMATION.

FDA's approval of Mitigare was arbitrary and capricious for an independent reason: The Mitigare label omits critical safety information FDA had previously concluded was necessary for all single-ingredient oral colchicine products. FDA's decision to approve a label that the agency itself once deemed deficient—on two separate grounds, no less—represents an unreasoned change in agency policy. *See Ramaprakash v. FAA*, 346 F.3d 1121, 1125 (D.C. Cir. 2003) ("An agency's failure to come to grips with conflicting precedent constitutes an inexcusable departure from the essential requirement of reasoned decision making.") (internal quotation marks omitted).

A. FDA Previously Required Colchicine Labels To Include Dose Adjustments Related To Drug-Drug Interactions.

Because of the importance of proper colchicine dosage, Mutual conducted studies to assess the effects of concomitant drug use, particularly with clarithromycin. *See supra* pp. 7-8. It then created a detailed chart of dose adjustments to offset the increased colchicine levels caused by drug-drug interactions. JA134-135. The Colcrys label suggests dose adjustments both for the actual drugs studied and for other drugs similar to the studied drugs. For example, the chart lists the toxicity results for clarithromycin, a strong CYP3A4 inhibitor,

and warns that similar effects are "anticipated with other strong CYP3A4 inhibitors." JA134.

FDA not only approved the detailed Colcrys label; it issued a Safety Alert explaining the importance of the dose adjustments. According to the Alert, "FDA concludes there is a risk for severe drug interactions in certain patients treated with colchicine and concomitant P-gp or strong CYP3A4 inhibitors. . . . The FDA-approved prescribing information for Colcrys contains recommended dosage adjustments." JA127. FDA reiterated its concerns in 2010, warning that the agency would take enforcement action against unapproved colchicine products, in part because their labeling "likely does not contain appropriate dosing and drug interaction information." 75 Fed. Reg. at 60768-70. In 2011, FDA repeated the same unequivocal determination in response to Mutual's Citizen Petition: "[P]roduct 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." JA670 (emphases added); *see also* JA686-687. The agency's consistent conclusion accords with general FDA regulations requiring that drug labels describe "clinically significant" drug-drug interactions. 21 C.F.R. § 201.57(c)(13)(i)(C).

Mitigare is a single-ingredient oral colchicine product, and thus plainly covered by these FDA pronouncements. But the Mitigare label contains only a

general warning that, if Mitigare is co-administered with a CYP3A4 or P-gp inhibitor, "reduced daily dose should be considered and the patient should be monitored for colchicine toxicity." JA699. That is a dramatic departure from FDA's repeated admonition about the need for clear dose adjustments.

FDA offered "only a partial, and ultimately inadequate, explanation" for breaking from its past position and allowing Hikma to omit specific dose adjustments. *Comms. & Control, Inc. v. FCC*, 374 F.3d 1329, 1336 (D.C. Cir. 2004). [redacted]

Fair enough. [redacted]

[redacted]

Mutual's data and dosing adjustments, which FDA believed were critical to preventing unnecessary deaths just a few years before, still apply to drugs—like clarithromycin—that Mutual showed interact with colchicine. So while FDA might have reasonably concluded that [redacted], it has never explained why specific dose modifications were unwarranted for the drugs used in *Mutual's* studies. There is no reasoned explanation anywhere in the record for why dose adjustments must be treated as an all-or-nothing proposition.

[2] Lest there be any doubt about the continuing validity of Mutual's drug-drug interaction studies, FDA requires the Colcrys dose adjustments on the labeling of protease inhibitors approved for the treatment of HIV. JA172. And the American College of Rheumatology's Guidelines for the Management of Gout continue to point healthcare providers to the Colcrys label for dose adjustments. JA1039.

B. FDA Previously Required Colchicine Labels To Inform Healthcare Providers About A Low-Dose Treatment Regimen.

In addition to studying drug-drug interactions, Mutual studied whether a low-dose colchicine regimen is effective for treating acute gout flares. The AGREE trial revealed that a low-dose regimen is just as effective as the traditional high-dose regimen, but results in significantly fewer adverse effects.

The approved Colcrys label applies the data from the AGREE trial by recommending a maximum dose of 1.8 mg over a one-hour period. JA132. It cautions that "[h]igher doses have not been found to be more effective." *Id.* As it did with the drug-drug interaction studies, FDA advised healthcare professionals in a Safety Alert that they should "refer to Colcrys' approved prescribing information for specific dosing recommendations." JA126. Again, FDA repeated the conclusion in response to Mutual's Citizen Petition: "[T]he 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." JA670 (emphasis added); *see also* JA691. The agency did not restrict this rule to colchicine products that, like Colcrys, are approved for *both* prophylaxis of gout flares and treatment of acute flares. Rather, it imposed a general requirement for any "single-ingredient colchicine product seeking approval for prophylaxis of gout flares"—a category that indisputably includes Mitigare.

That determination cannot be dismissed as inadvertently overbroad. FDA expressly considered "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. FDA concluded that even a drug indicated for prophylaxis alone would be unsafe if it omitted information about the treatment of acute flares. *Id.* (citing 21 C.F.R. § 314.127(a)(7)). To drive the point home, FDA cited a prior Citizen Petition Response in which it had similarly determined that a drug indicated for a high-risk population could not be approved without safety information geared toward low- and moderate-risk populations. After all, patients might move from a higher-risk category to a lower-risk category. JA691 n.75 (citing FDA Resp. to Dkt. No. 2003P-0518 (Sept. 20, 2004) (Rapamune Petition Response)). By analogizing to the Rapamune Petition Response, FDA indicated that patients taking colchicine for prophylaxis naturally take it for acute flares as well—which, of course, is the case.

Yet, despite its clear statements in response to Mutual's Citizen Petition, FDA allowed Hikma to omit any mention of a low-dose colchicine regimen from the Mitigare label. Instead, the label states only that the "safety and effectiveness of MITIGARE for acute treatment of gout flares during prophylaxis has not been studied." JA699. The District Court blessed the agency's abrupt change in policy,

finding it "well-supported" by the administrative record. JA90 (citing JA773). Not quite. Here is the sole relevant statement on which the District Court relied:

[redacted]

There are several problems with the District Court's reliance on this single statement. *First*, FDA made no attempt to reconcile this statement with its response to Mutual's Citizen Petition, which specifically stated that single-ingredient colchicine products indicated for prophylaxis of gout flares must include information about a low-dose regimen. Despite its "obvious relevance," FDA "failed even to mention or discuss, let alone distinguish," its prior position. *Lone Mtn. Processing, Inc. v. Sec'y of Labor*, 709 F.3d 1161, 1164 (D.C. Cir. 2013); *see also FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009) ("[T]he requirement that an agency provide reasoned explanation for its action would ordinarily demand that it display awareness that it *is* changing position.").

Second, FDA's single statement on the subject does not accurately describe the Mitigare label. *See Fox v. Clinton*, 684 F.3d 67, 78 (D.C. Cir. 2012) (finding agency decision arbitrary and capricious in part because "it appears to be based on . . . possible misunderstandings of the material facts in this case"). The label does

not warn that [redacted]. It employs far more ambiguous language, blandly observing that the "safety and effectiveness of MITIGARE for acute treatment of gout flares during prophylaxis *has not been studied*." JA699 (emphasis added). So even this lone record statement cannot save FDA here.

Third, the additional gloss that FDA and the District Court placed on the agency's decision amounts to an impermissible *post-hoc* rationalization. *See Motor Vehicle Mfrs. Ass'n of United States v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 50 (1983) (an "agency's action must be upheld, if at all, on the basis articulated by the agency itself"). The District Court suggested that information about a low-dose regimen "might confuse users into taking more Mitigare," because "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." JA90. The District Court's concern about consumer confusion is nowhere to be found in the brief statement it cited. [redacted]; *see also* JA691 & n.75.

The bottom line is this: FDA twice departed from clear precedent without reason, or for incomplete reasons, or for reasons it had previously rejected. The APA demands more. FDA's approval of Mitigare should be rescinded.

CONCLUSION

For the foregoing reasons, the District Court's decision should be reversed and the case remanded with instructions to enter an order granting Takeda's motion for summary judgment.

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Respectfully submitted,

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ADDENDUM

PERTINENT STATUTES & REGULATIONS

Page

STATUTES:

REGULATIONS:

21 U.S.C. § 355(a). New drugs—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) or (j) of this section is effective with respect to such drug.

21 U.S.C. § 355(b). New drugs—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.

(4)(A) An applicant may not amend or supplement an application referred to in paragraph (2) to seek approval of a drug that is a different drug than the drug identified in the application as submitted to the Secretary.

(B) With respect to the drug for which such an application is submitted, nothing in this subsection or subsection (c)(3) of this section prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(5)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 262 of title 42, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 262 of title 42 if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size—

(i)(I) of clinical trials intended to form the primary basis of an effectiveness claim; or

(II) in the case where human efficacy studies are not ethical or feasible, of animal and any associated clinical trials which, in combination, are intended to form the primary basis of an effectiveness claim; or

(ii) with respect to an application for approval of a biological product under section 262(k) of title 42, of any necessary clinical study or studies.

The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request.

(C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 262 of title 42 (including all scientific and medical matters, chemistry, manufacturing, and controls).

(6) An application submitted under this subsection shall be accompanied by the certification required under section 282(j)(5)(B) of title 42. Such certification shall not be considered an element of such application.

21 U.S.C. § 355(c). New drugs—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 U.S.C. § 355(j). New drugs—Abbreviated new drug applications.

(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

(2)(A) An abbreviated application for a new drug shall contain—

(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (7) (hereinafter in this subsection referred to as a ‘‘listed drug’’);

(ii)(I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;

(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of section 321(p) of this title, and such other information respecting the different active ingredient with respect to which the petition was filed as the Secretary may require; (iii) information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug referred to in clause (i) or, if the route of administration, the dosage form, or the strength of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), such information respecting the route of administration, dosage form, or strength with respect to which the petition was filed as the Secretary may require;

(iv) information to show that the new drug is bioequivalent to the listed drug referred to in clause (i), except that if the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that

the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in clause (i) and the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in clause (i);

(v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers;

(vi) the items specified in clauses (B) through (F) of subsection (b)(1) of this section;

(vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (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

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (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.

The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

* * *

35 U.S.C. § 271(e). Infringement of patent.

* * *

(2) It shall be an act of infringement to submit—

(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent,

(B) an application under section 512 of such Act or under the Act of March 4, 1913 (21 U.S.C. 151–158) for a drug or veterinary biological product which is not primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques and which is claimed in a patent or the use of which is claimed in a patent, or

(C)(i) with respect to a patent that is identified in the list of patents described in section 351(l)(3) of the Public Health Service Act (including as provided under section 351(l)(7) of such Act), an application seeking approval of a biological product, or

(ii) if the applicant for the application fails to provide the application and information required under section 351(l)(2)(A) of such Act, an application seeking approval of a biological product for a patent that could be identified pursuant to section 351(l)(3)(A)(i) of such Act,

if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug, veterinary biological product, or biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

* * *

21 C.F.R. § 201.57(c). Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).

Full prescribing information. The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings, subheadings, and identifying numbers required under § 201.56(d)(1), unless omitted under § 201.56(d)(4). If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with § 201.56(d)(2).

* * *

(13) *12 Clinical pharmacology*. (i) This section must contain information relating to the human clinical pharmacology and actions of the drug in humans. Pharmacologic information based on in vitro data using human biomaterials or pharmacologic animal models, or relevant details about in vivo study designs or results (e.g., drug interaction studies), may be included in this section if essential to understand dosing or drug interaction information presented in other sections of the labeling. This section must include the following subsections:

* * *

(C) *12.3 Pharmacokinetics*. This subsection must describe the clinically significant pharmacokinetics of a drug or active metabolites, (i.e., pertinent absorption, distribution, metabolism, and excretion parameters). Information regarding bioavailability, the effect of food, minimum concentration (Cmin), maximum concentration (Cmax), time to maximum concentration (Tmax), area under the curve (AUC), pertinent half-lives (t1/2), time to reach steady state, extent of accumulation, route(s) of elimination, clearance (renal, hepatic, total), mechanisms of clearance (e.g., specific enzyme systems), drug/drug and drug/food (e.g., dietary supplements, grapefruit juice) pharmacokinetic interactions (including inhibition, induction, and genetic characteristics), and volume of distribution (Vd) must be presented if clinically significant. Information regarding nonlinearity in pharmacokinetic parameters, changes in pharmacokinetics over time, and binding (plasma protein, erythrocyte) parameters must also be presented if clinically significant. This section must also include the results of pharmacokinetic studies (e.g., of metabolism or interaction) that establish the absence of an effect, including pertinent human studies and in vitro data. Dosing

recommendations based on clinically significant factors that change the product's pharmacokinetics (e.g., age, gender, race, hepatic or renal dysfunction, concomitant therapy) that appear in other sections (e.g., "Warnings and Precautions," "Dosage and Administration" or "Use in Specific Populations") must not be repeated in this subsection, but the location of such recommendations must be referenced.

* * *

21 C.F.R. § 314.127(a). Applications for FDA Approval to Market a New Drug—Refusal to approve an abbreviated new drug application.

FDA will refuse to approve an abbreviated application for a new drug under section 505(j) of the act for any of the following reasons:

* * *

(7) Information submitted in the abbreviated new drug application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the abbreviated new drug application except for changes required because of differences approved in a petition under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers or because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use.

* * *

CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. P. 32(a)(7)(C), I hereby certify that this Opening Brief for Appellant complies with the type-volume limitation of this Court's July 1, 2015 Order because the brief contains 6,973 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii) and Circuit Rule 32(e)(1).

I further certify that this brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because the brief has been has been prepared in Times New Roman 14-point font using Microsoft Word 2010.

/s/ Catherine E. Stetson
Catherine E. Stetson

Counsel for Appellant Takeda Pharmaceuticals U.S.A., Inc.

CERTIFICATE OF SERVICE

I hereby certify that on August 17, 2015, the foregoing Opening Brief for Appellant was electronically filed through this Court's CM/ECF system, which will send a notice of filing to all registered users.

/s/ Catherine E. Stetson
Catherine E. Stetson

Counsel for Appellant Takeda Pharmaceuticals U.S.A., Inc.