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., *et al.*

Plaintiffs-Appellants,

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.*,

Intervenors-Defendants.

On appeal from the United States District Court for the District of Columbia, No. 1:14-cv-1850 (K. Jackson, J.)

BRIEF OF *AMICUS CURIAE* PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA IN SUPPORT OF APPELLANTS

Robert A. Long
Krista H. Carver
Kevin King
COVINGTON & BURLING LLP
850 10th Street NW
Washington, DC 20001
Telephone: (202) 662-6000
rlong@cov.com

August 24, 2015

Attorneys for Amicus Curiae Pharmaceutical Research and Manufacturers of America

CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES

Pursuant to D.C. Circuit Rule 28(a)(1), counsel for Amicus Curiae Pharmaceutical and Research Manufacturers of America ("PhRMA") hereby certify as follows:

A. Parties and Amici. All parties and intervenors that appeared in the district court are listed in the Brief of Appellant Takeda Pharmaceuticals U.S.A., Inc. That Brief also lists all parties and intervenors appearing in this Court.

B. Ruling Under Review. The ruling under review is the January 12, 2015 opinion issued by the district court.

C. Related Cases. PhRMA is not aware of any related cases pending before this Court or any other court.

/s/ Robert A. Long

Robert A. Long
COVINGTON & BURLING LLP
850 10th Street NW
Washington, DC 20001

Attorney for Amicus Curiae Pharmaceutical Research and Manufacturers of America

Dated: August 24, 2015

DISCLOSURE STATEMENT

Pursuant to Rule 26.1 of the Federal Rules of Appellate Procedure and Circuit Rule 26.1, Amicus Curiae Pharmaceutical Research and Manufacturers of America ("PhRMA") states that it is a trade association with no parent corporation. No publicly held corporation has a 10% or greater ownership interest in PhRMA. PhRMA's member companies are listed on its website at http://www.phrma.org.

/s/ Robert A. Long

Robert A. Long
COVINGTON & BURLING LLP
850 10th Street NW
Washington, DC 20001

Attorney for Amicus Curiae Pharmaceutical Research and Manufacturers of America

Dated: August 24, 2015

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES*

CASES **PAGE(S)**

STATUTES

---

* Authorities upon which we chiefly rely are marked with asterisks.

REGULATORY MATERIALS

OTHER AUTHORITIES

GLOSSARY

ANDA	Abbreviated New Drug Application
DESI	Food and Drug Administration's Drug Efficacy Study Implementation program
FDA	United States Food and Drug Administration
NDA	New Drug Application
PhRMA	Pharmaceutical Research and Manufacturers of America

STATEMENT OF AMICUS CURIAE[1]

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary, nonprofit association representing the nation's leading research-based pharmaceutical and biotechnology companies. PhRMA's member companies are dedicated to discovering medicines that enable patients to lead longer, healthier, and more productive lives. During 2014 alone, PhRMA members invested an estimated $51.2 billion in efforts to research and develop new medicines. PhRMA's mission is to advocate public policies that encourage the discovery of life-saving and life-enhancing medicines. This mission includes a strong interest in how courts resolve issues that have broad, industry-wide significance. Accordingly, PhRMA regularly participates as an amicus curiae in such cases, bringing an industry perspective to bear. The issues in this appeal could affect the rights of all companies that develop innovative drugs, and therefore have particular industry-wide significance.

[1] No party's counsel authored this brief in whole or in part. No party or a party's counsel made a monetary contribution intended to fund the preparation or submission of this brief, and no person other than amicus curiae, its members, or its counsel made such a monetary contribution. All parties have consented to the filing of this amicus brief.

SUMMARY OF ARGUMENT

The Hatch-Waxman Act embodies a grand bargain that balances the concerns of two groups of drug manufacturers: those who produce pioneer drugs and those who produce follow-on drugs.[2] The Act preserves pioneer manufacturers' incentives to develop innovative new drugs by incorporating exclusivity and patent protections into the drug-approval process and codifying protections for clinical data. At the same time, the Act provides follow-on manufacturers with a shortcut to market by allowing them to obtain approval for versions of brand-name drugs without conducting their own safety and efficacy studies. Each benefit under the Act comes with a parallel burden: pioneer manufacturers must allow follow-on manufacturers to piggyback on their research efforts, and follow-on manufacturers may rely on those efforts only after following procedures that preserve pioneer manufacturers' incentives.

For 30 years, the Food and Drug Administration (FDA) has applied the Hatch-Waxman Act in a way that effectuates this bargain. Agency regulations generally require follow-on manufacturers to use the "abbreviated new drug application" procedure, which includes detailed protections for pioneer

[2] In this brief, "pioneer drug" refers to new brand-name drugs; "follow-on drug" refers to drugs approved under sections 505(b)(2) and 505(j) of the Act. Follow-on drugs include "generic" drugs that are duplicates of a previously approved brand-name drug, as well as drugs approved under section 505(b)(2) that are similar to (but not duplicates of) a previously approved brand-name drug.

manufacturers' rights, when that procedure is available. When follow-on manufacturers invoke an alternative procedure under section 505(b)(2) of the Act, FDA likewise requires the applicants to provide appropriate patent certifications, including when the applicant implicitly relies on a pioneer drug's prior approval. FDA also protects pioneer manufacturers by allowing follow-on applicants to rely only on the fact of a pioneer drug's prior approval and not on the confidential clinical data underlying that approval.

The district court's decision undermines Hatch-Waxman's grand bargain by permitting section 505(b)(2) applicants to obtain the Act's benefits without shouldering any of the corresponding burdens. Specifically, the district court concluded that a section 505(b)(2) applicant may obtain approval of a follow-on drug—without providing the required patent certification—by omitting any mention of the pioneer drug in its application and relying on FDA to fill in the blanks.

That interpretation cannot be squared with the Act's structure and purpose. On average, it takes 10 to 15 years and nearly $2.6 billion to develop a pioneer drug. There would be little reason for pioneer manufacturers to make such enormous investments if FDA could turn around and use the resulting data to approve competitors' section 505(b)(2) applications without affording pioneer manufacturers any of the Hatch-Waxman Act's protections. Properly understood,

the Act requires a patent certification whenever FDA's prior finding that a pioneer drug is safe and effective is essential to approval of a section 505(b)(2) application.

The decision below also conflicts with FDA's regulations and guidance. *First*, the district court assumed that a section 505(b)(2) applicant "relie[s] upon" one and only one pioneer drug, but FDA has made clear that section 505(b)(2) applications may rely on more than one drug. *Second*, the district court incorrectly concluded that a section 505(b)(2) applicant faces no constraints in deciding which pioneer drug (or drugs) it will "rel[y] upon." While applicants have some freedom of choice, FDA has limited that flexibility by concluding that a section 505(b)(2) application may *implicitly* rely upon a similar pioneer drug. *Third*, the district court failed to observe the rule that a section 505(b)(2) applicant may rely on the fact of a pioneer drug's approval, but not the confidential data underlying that approval.

The judgment below should be reversed.

ARGUMENT

I. The Hatch-Waxman Act Enacted A Grand Bargain.

A. Prior to 1984, There Was Dissatisfaction With FDA's Drug Approval Process.

The Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040, established a premarket notification regime for "new" drugs. Under the 1938 Act, a manufacturer could not introduce into interstate commerce any new

drug unless the manufacturer first filed a new drug application (NDA) that included "full reports of investigations" indicating "whether or not such drug [was] safe for use." 1938 Act § 505(b). The 1938 Act did not provide a separate mechanism for approving copies of pioneer drugs.

In 1962, Congress converted the notification system to the modern premarket approval system and added a requirement that NDAs demonstrate a new drug's effectiveness as well as its safety. *See* Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780. At Congress's direction, FDA established the Drug Efficacy Study Implementation (DESI) program to determine whether new drugs introduced between 1938 and 1962 met the effectiveness requirement. *See* 1962 Act § 107.

The DESI program led FDA to create a separate, simplified approval process for generic drugs. *See* 35 Fed. Reg. 6,574 (1970). This "abbreviated new drug application" (ANDA) procedure "was designed to assure that generic copies containing [DESI-approved] active ingredients were as safe and effective as the pioneer drug." Ellen J. Flannery & Peter Barton Hutt, *Balancing Competition and Patent Protection in the Drug Industry: The Drug Price Competition and Patent Term Restoration Act of 1984*, 40 Food Drug Cosmetic L.J. 269, 274 (1985) ("*Balancing Competition*"). ANDA applicants were required to demonstrate "bioequivalence"—*i.e.*, that the generic drug would have "the same therapeutic

effect as the pioneer drug product"—but did not have to make the broader safety and effectiveness showing needed for approval of a pioneer drug. *Ibid.*

The ANDA procedure had a major limitation: It applied only to copies of drugs introduced before 1962 that had been deemed effective under the DESI program. Thus, manufacturers could not use an ANDA to obtain approval of generic copies of pioneer drugs that were introduced after 1962. *See id.* at 274–75.

In 1980, FDA adopted a "paper NDA" policy that applied to all pioneer drugs—whether introduced before or after 1962. *See* 45 Fed. Reg. 82,052 (1980); 46 Fed. Reg. 27,396 (1981). Paper NDAs combined elements of the NDA and ANDA approval procedures. *See* Peter Barton Hutt *et al.*, Food and Drug Law 1012 (4th ed. 2014). Paper NDA applicants, like traditional NDA applicants, had to establish the drug's safety and effectiveness. Unlike traditional NDA applicants, however, paper NDA applicants could rely on published scientific literature concerning the drug's safety and effectiveness rather than conducting clinical studies and trials of their own. *Balancing Competition*, *supra*, at 275. FDA could approve a follow-on drug in this fashion "any time after approval of the pioneer NDA," so long as the literature cited in the paper NDA "was reliable and sufficient to establish the safety and effectiveness of the drug." *Ibid.*

Pursuant to the paper NDA policy, "unpublished safety and effectiveness data submitted as part of a pioneer drug's NDA" could not "be released to the

public or used to support another manufacturer's NDA." *Ibid.*; *see also* 46 Fed. Reg. at 27,396 ("[N]o data in the NDA can be utilized to support another NDA without express permission of the original NDA holder."). This restriction accorded with FDA's longstanding view that clinical data submitted in an NDA are confidential trade secrets belonging solely to the applicant. *See* 37 Fed. Reg. 9,128, 9,130–31 (1972); 39 Fed. Reg. 44,602, 44,634–38 (1974); 45 Fed. Reg. 82,053, 82,058 (1980).

By the early 1980s, industry participants on all sides were dissatisfied with aspects of FDA's drug-approval regime. Pioneer manufacturers "were frustrated . . . that much of their products' patent life was consumed before they could even legally market the drugs, because of the prolonged nature of the NDA approval process." Food and Drug Law, *supra*, at 1001. In addition, FDA's procedures for approving follow-on drugs did not take account of patent protection for the underlying pioneer drug, creating the possibility that a follow-on drug would receive FDA approval before the pioneer drug's patent term expired. Follow-on manufacturers, for their part, were dissatisfied with their inability to use the ANDA procedure for copies of post-1962 pioneer drugs. *Id.* at 1000–01. Paper NDAs were an imperfect solution to this problem, given the lack of published scientific literature on most post-1962 pioneer drugs. *See* H.R. Rept. 98-857, Pt. I, 98th Cong., 2d Sess., at 16 (1984) ("House Report").

B. The Hatch-Waxman Act Balanced The Interests Of Pioneer Manufacturers and Follow-On Applicants.

In the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984)—better known as the Hatch-Waxman Act—Congress addressed these issues by striking "a grand bargain between the generic and pioneer drug industries." Food and Drug Law, *supra*, at 1000; *see also Teva Pharm. Indus. Ltd. v. Crawford*, 410 F.3d 51, 54 (D.C. Cir. 2005) ("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."). Three elements of Hatch-Waxman's grand bargain are relevant to this case.

1. The Act Protects Pioneer Manufacturers' Confidential Data And Patent Rights.

Congress sought to preserve incentives to develop pioneer drugs by providing new forms of regulatory protection to pioneers.

The 1962 amendments "increased dramatically" the cost and time required to develop pioneer drugs. S. Rept. 97-138, 97th Cong., 1st Sess., at 2 (1981). Because the approval process took years to complete, the pioneer manufacturer's 17-year patent monopoly was significantly shortened. *Ibid.* Meanwhile, the cost to test, evaluate, and secure FDA approval of pioneer drugs skyrocketed from "approximately $4 million in 1962 to approximately $70 million" by the early 1980s. *Ibid.* These developments reduced manufacturers' incentives to develop

new drugs. *Ibid*. Manufacturers had little reason to invest the resources needed to bring a pioneer drug to market if competitors could sell copies of the drug "at a fraction of the cost" just a few years later. Food and Drug Law, *supra*, at 1013.

Congress responded to this problem in several ways. It provided periods of regulatory exclusivity for pioneer drugs, separate and apart from any applicable patent protection. *See id.* at 1003. For example, an ANDA seeking approval for a copy of a pioneer drug generally may not be submitted for five years following the approval of a pioneer NDA. 21 U.S.C. § 355(j)(5)(F)(ii).

Congress also recognized that the safety and effectiveness data in pioneer NDAs result from large, long-term investments. If competitors could use the data to gain immediate approval of follow-on drugs, pioneer manufacturers would have little incentive to conduct such expensive trials in the first place. *See Webb v. Dep't of Health & Human Servs.*, 696 F.2d 101, 102 (D.C. Cir. 1982). To address this issue, the Hatch-Waxman Act provided that "safety and effectiveness data" submitted as part of a pioneer NDA will "retain their status as trade secrets and confidential commercial information" unless one of five carefully-demarcated exceptions applies. Food and Drug Law, *supra*, at 1002. For example, proprietary data may be disclosed if the NDA has been abandoned by its sponsor, or if the NDA "is not approvable and all legal appeals have been exhausted." 21 U.S.C. § 355(*l*)(A)–(B). Even when one of the exceptions applies, FDA may not disclose

the information in "extraordinary circumstances," *id.* § 355(*l*), such as when the data "retain . . . commercial, competitive value," 130 Cong. Rec. 24,977 (Sept. 12, 1984) (statement of Sen. Hatch); *see also* 21 U.S.C. § 331(j) (barring unauthorized use of "any information" submitted in a NDA "which as a trade secret is entitled to protection"); 18 U.S.C. § 1905 (establishing criminal penalties for federal employees who divulge trade secrets "in any manner . . . not authorized by law").

These protections codified FDA's longstanding policy that safety and effectiveness data in a pioneer NDA generally "cannot be released to the public *or used to approve a generic drug*." Food and Drug Law, *supra*, at 1002 (emphasis added); *see also Balancing Competition*, *supra*, at 275–76. Indeed, the House Report accompanying the Hatch-Waxman Act explained that Congress "d[id] not intend to change other regulations regarding . . . trade secrets, and confidentiality of IND, NDA and master file safety and effectiveness information and data." House Report, *supra*, at 36.

The Hatch-Waxman Act also provided additional protection for pioneer manufacturers' patent rights. When a pioneer manufacturer files a NDA, it must include "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 using such drug." 21 U.S.C. § 355(b)(1). FDA compiles this information in

Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the "Orange Book."

Before seeking FDA approval of a follow-on drug, follow-on manufacturers must consult the Orange Book and provide a certification with respect to each listed patent in their applications. The applicant may certify that no patents are listed, that any listed patents have expired, or that the applicant will "market [its drug] beginning when any still-in-force patents expire." *FTC v. Actavis, Inc.*, 133 S.Ct. 2223, 2228 (2013) (citing 21 U.S.C. § 355(j)(2)(A)(vii)); *see also* 21 U.S.C. § 355(b)(2)(A). Alternatively—and of critical importance here—the applicant may certify that any patent for the pioneer drug "is invalid or will not be infringed by the manufacture, use, or sale" of the follow-on drug. *Ibid.* (citing 21 U.S.C. § 355(j)(2)(A)(vii)(IV)); *see also* 21 U.S.C. § 355(b)(2)(A)(iv).

This last mode of certification—known as a "Paragraph IV" certification—triggers a series of "special procedures for identifying, and resolving, related patent disputes." *Actavis*, 133 S.Ct. at 2228. The filing of such a certification is deemed to be an act of patent infringement. *See* 35 U.S.C. § 271(e)(2)(A). When a follow-on manufacturer files an application containing a Paragraph IV certification, it must promptly notify the patent owner and the holder of the pioneer NDA, who may then file an infringement suit against the applicant. *See* 21 U.S.C. §§ 355(b)(3), (c)(3)(C); 355(j)(2)(B), (j)(5)(B)(iii). If such a suit is filed within 45

days after the notice is received, FDA may not approve the follow-on manufacturer's application for 30 months, unless a court decides before that time that the patent is invalid or not infringed. *See* 21 U.S.C. §§ 355(j)(5)(B)(iii), 355(c)(3)(C).

These special procedures enable pioneer manufacturers to litigate patent infringement disputes *before* a follow-on drug is approved and brought to market, an event that sharply reduces the value of the pioneer drug. *See* Food and Drug Law, *supra*, at 1013–14.

2. The Act Provides Fast-Track Approval For Follow-On Drugs With Due Regard for Patent And Regulatory Exclusivity Rights.

The Hatch-Waxman Act also codified and extended FDA's ANDA policies in a way that enabled follow-on "drugs to be marketed more cheaply and quickly." *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990). This is the other side of Hatch-Waxman's "grand bargain."

Section 505(j) of the Act eliminated the restriction that ANDAs could only be used for copies of pioneer drugs introduced before 1962. 21 U.S.C. § 355(j); *Balancing Competition*, *supra*, at 277. As a result, follow-on manufacturers can file an ANDA with respect to *any* pioneer drug, subject to the protections outlined above. This change allowed "generic manufacturer[s] to obtain approval while avoiding the costly and time-consuming studies needed to obtain approval for a

pioneer drug," thereby "speed[ing] the introduction of low-cost generic drugs to market." *Actavis*, 133 S.Ct. at 2228 (citations and quotation marks omitted).

Most ANDAs seek approval to market a duplicate of a "listed" pioneer drug. ANDA sponsors need not provide clinical studies demonstrating the generic drug's safety and effectiveness. Instead, they must show that the generic drug is "the same" as the pioneer drug in terms of active ingredient(s), route of administration, dosage form, and other key features. 21 U.S.C. § 355(j)(2)(A)(i)–(iii). The sponsor must also show that the generic drug is "bioequivalent" to the pioneer drug—*i.e.*, that the "rate and extent of absorption do not show a significant difference . . . when administered . . . under similar experimental conditions." *Id.* § 355(j)(2)(A)(iv), (j)(8)(B)(i); 21 C.F.R. § 320.1(e).

The statute provides an alternative ANDA option for manufacturers that wish to market a drug that is *not* a duplicate of an existing pioneer drug. *See* 21 U.S.C. § 355(j)(2)(C). This option allows an applicant to seek approval for a drug that is the same as a pioneer drug in most respects, but "has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug." *Id.* To secure approval for such a drug, the manufacturer must first submit a "suitability petition" to FDA "seeking permission to file" an ANDA. *Id.* This petition must show that "the change from the pioneer drug . . . may be adequately evaluated for approval as safe and effective without the animal

and clinical information required for a pioneer NDA." *Balancing Competition*, *supra*, at 279–80. If FDA finds that the manufacturer has met this burden, it allows the manufacturer to file a "petitioned" ANDA. *See id.* at 280. If FDA rejects the manufacturer's suitability petition, the manufacturer must seek approval under section 505(b)(2) or file a full NDA. *See* Food and Drug Law, *supra*, at 1001.

Congress codified aspects of FDA's pre-1984 "paper NDA" policy in section 505(b)(2) of the Act. *See* 21 U.S.C. § 355(b)(2). As interpreted by FDA, section 505(b)(2) represents a "mid-way" point "between a full NDA and an abbreviated NDA." Food and Drug Law, *supra*, at 1012. Section 505(b)(2) applications are submitted under section 505(b)(1)—"the same provisio[n] of the [statute] which govern[s] full NDAs"—and thus the applicant must make a complete showing of the drug's safety and effectiveness. *Balancing Competition*, *supra*, at 296. However, FDA has concluded that the applicant may satisfy this obligation by relying on two classes of information not available to traditional NDA applicants: (1) published scientific literature regarding the drug's safety and effectiveness, and (2) "FDA's own previous finding of safety and effectiveness for" a similar pioneer drug. Food and Drug Law, *supra*, at 1012. In statutory terms, the section 505(b)(2) applicant may demonstrate safety and effectiveness by relying on "investigations . . . [that] were not conducted by or for the applicant and

for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." 21 U.S.C. § 355(b)(2).

FDA has tailored the section 505(b)(2) application process to instances in which a follow-on drug shares similarities with an existing pioneer drug, but differs in indication or other features to such an extent that "investigations, other than bioavailability or bioequivalence studies, are essential to the [follow-on drug's] approval." 21 C.F.R. § 314.54(a). Thus, FDA advises that "[a]n applicant should file a 505(b)(2) application" when it seeks to modify a pioneer drug in ways that would prevent the applicant from filing an ANDA. FDA, *Guidance for Industry: Applications Covered by Section 505(b)(2) – Draft Guidance*, at 3 (1999), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/ucm079345.pdf ("*Draft Guidance*"). For example, a section 505(b)(2) application "should be filed" when a manufacturer seeks "to change a prescription (Rx) indication to an over-the-counter (OTC) indication." *Id.* at 4.

Section 505(b)(2) applications must "identif[y] . . . the listed drug for which FDA has made a finding of safety and effectiveness and on which finding the applicant relies in seeking approval of its proposed drug product." 21 C.F.R. § 314.54(a)(1)(iii). The applicant may establish that the elements of its drug that are present in the pioneer drug (e.g., the active ingredient) are safe and effective by

relying on FDA's prior approval of the pioneer drug. *See* Food and Drug Law, *supra*, at 1012. However, the applicant must also provide additional data—whether in the form of published scientific literature or its own original studies—to "support the difference[(s)]" from the pioneer drug. *Ibid.* These bridging data must establish that the modifications do not compromise the product's safety and effectiveness. For instance, the section 505(b)(2) applicant might conduct additional studies to show the drug is safe and effective in a new indication for which the pioneer drug is not approved.

C. FDA Has Applied The Hatch-Waxman Act In A Way That Effectuates The Grand Bargain.

For 30 years, FDA has sought to apply the Hatch-Waxman Act in a manner that effectuates and reinforces the grand bargain struck by Congress.

1. FDA Requires Follow-On Manufacturers To Use An ANDA If A Drug Qualifies For ANDA Approval.

FDA regulations provide that ANDAs are the primary means for approving follow-on drugs. "FDA may refuse to file an application . . . if . . . [t]he application is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act." 21 C.F.R. § 314.101(d)(9). In other words, if a follow-on drug *can* be approved through an ANDA, it generally *must* be approved through an ANDA. *See* 57 Fed. Reg. 17,950, 17,956 (1992) ("As a matter of policy, the agency does not accept

applications under section 505(b)(2) of the act when there is a listed drug that would provide a basis for an application under section 505(j) of the act.").[3]

FDA's policy serves an important purpose: It prevents follow-on manufacturers from "circumvent[ing]" the Hatch-Waxman Act's patent and regulatory exclusivity protections for pioneer drugs. *See* FDA Response Re: Docket No. FDA-2010-P-0614, at 14 (May 25, 2011) ("*Colchicine Citizen Petition Response*").[4] When a follow-on drug is identical to, or involves only "minor variations" from, a pioneer drug, the follow-on manufacturer must file an ANDA. 21 C.F.R. § 314.101(d)(9). If the applicant seeks to market its drug during the term of a listed patent, the ANDA must contain a certification that the patent is invalid or that the proposed drug does not infringe the pioneer-drug patents, and FDA will not accept or approve the ANDA if the pioneer drug is subject to a period of regulatory exclusivity. Moreover, if the ANDA applicant makes a Paragraph IV certification, it must notify the pioneer NDA holder and patent owner and risk a 30-month stay of the follow-on drug's final approval.[5]

---

[3] The lone exception to this rule involves drugs that differ sufficiently from the pioneer drug that the sponsor would need to file a suitability petition before filing an ANDA. *Draft Guidance*, *supra*, at 4. For those drugs, the sponsor may use either an ANDA or a section 505(b)(2) NDA. 57 Fed. Reg. at 17,952 (1992).

[4] Each of the citizen petition responses cited in this brief is available by docket number on www.regulations.gov.

[5] FDA applied its policy in this very case. West-Ward filed a section 505(b)(2) application for a colchicine tablet that was nearly identical to Takeda's FDA-(continued…)

2. FDA Allows Section 505(b)(2) Applicants To Rely On The Fact Of A Pioneer Drug's Approval, But Not On The Underlying Clinical Data.

In accordance with its longstanding confidentiality policy, FDA has allowed follow-on applicants, and particularly section 505(b)(2) applicants, to rely on the *fact* of a prior NDA approval, but not on the proprietary *data* underlying that approval. A section 505(b)(2) applicant may demonstrate the safety and efficacy of its proposed drug by citing a previously approved pioneer drug and relying on FDA's "finding of safety and effectiveness" with respect to that drug. 21 C.F.R. § 314.54(a)(1)(iii).[6] FDA has insisted, however, that section 505(b)(2) applicants may not rely on the clinical studies and proprietary data contained in the underlying pioneer NDA. In 2003, for example, FDA explained that "[r]eliance on FDA's conclusion that an approved drug is safe and effective does not involve" use "of the data in the listed drug's NDA." *Consolidated 505(b)(2) Citizen Petition Response*, *supra*, at 15. "Although reliance on an FDA finding of safety and effectiveness for an NDA is certainly indirect reliance on the data submitted in the original NDA, reliance on the conclusions supported by that data is not the same as

---

approved Colcrys product. Takeda's predecessor-in-interest objected, arguing that West-Ward's tablet must be approved, if at all, through an ANDA. *Colchicine Citizen Petition Response*, *supra*, at 11–12. FDA agreed. *See id.* at 16–17.

[6] *See also* FDA Response Re: Docket Nos. 2001P-0323/CP1 & C5 et al., at 3 (Oct. 14, 2003) ("*Consolidated 505(b)(2) Citizen Petition Response*"); FDA Response Re: Docket Nos. 2004P-0231/CP1 et al., at 38 (May 30, 2006) ("*Omnitrope Citizen Petition Response*"); *Colchicine Citizen Petition Response*, *supra*, at 10.

manipulating those data to reach new conclusions not evident from the existing approval." *Id.* at 10 n.14. Accordingly, "if the NDA for the listed drug contained studies indicating that the drug may be effective for indications X and Y, but the listed drug is not approved for use Y, a 505(b)(2) applicant could not rely on those studies to get approval for indication Y; it could only rely on the fact that the Agency found the drug to be effective for use X." *Ibid.*[7]

FDA's bright-line distinction between the fact of FDA approval and the underlying data effectuates the Hatch-Waxman Act's grand bargain. It promotes the availability of low-cost follow-on drugs "by allowing the generic to piggy-back on the pioneer's approval efforts," *Actavis*, 133 S.Ct. at 2228, while also preserving pioneer manufacturers' incentives to innovate by ensuring that data included in an NDA are held in confidence.

3. FDA Requires Section 505(b)(2) Applicants To Provide Appropriate Patent Certifications.

FDA's interpretation of section 505(b)(2)'s patent-certification requirements also upholds the grand bargain. As explained above, when the Orange Book lists an unexpired patent for the pioneer drug, a section 505(b)(2) applicant must

[7] *See also* FDA Response Re: Docket No. 2004P-0386/CP1 & RC1, at 8 (Nov. 30, 2004) ("*Fenofibrate Citizen Petition Response*") ("FDA's longstanding interpretation of the statute does not permit 505(b)(2) applicants to rely on particular investigations in previously approved NDAs that are not reflected in the NDA approvals."); *Omnitrope Citizen Petition Response*, *supra*, at 37 ("[U]se of the 505(b)(2) pathway does not entail disclosure of trade secret or confidential commercial information, nor does it involve unauthorized reliance on such data.").

include either a certification that the applicant does not seek approval until the patent expires, or a Paragraph IV certification that the patent "is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted." 21 U.S.C. § 355(b)(2)(A)(iii)–(iv). From the applicant's standpoint, both options have potential disadvantages. The former requires the applicant to delay marketing its product until the patent expires, while the latter "often means provoking litigation." *Actavis*, 133 S.Ct. at 2228 (quotation marks omitted). As a result, section 505(b)(2) applicants have an incentive to avoid citing, as listed drugs, pioneer drugs that remain subject to patent protection—even when such drugs are similar to the proposed drug and such patents might be infringed. Taken to its extreme, allowing section 505(b)(2) applicants to avoid such citations would "circumvent" the Act's "patent certification obligations." *Fenofibrate Citizen Petition Response*, *supra*, at 11 n.15.

FDA has addressed when a section 505(b)(2) application "relies" on a pioneer drug's approval. The governing regulation states that a section 505(b)(2) applicant must "identif[y] . . . the listed drug for which FDA has made a finding of safety and effectiveness and on which finding the applicant relies." 21 C.F.R. § 314.54(a)(1)(iii). The applicant must also submit a certification "with respect to any relevant patents that claim the listed drug or that claim any other drugs on which investigations relied on by the applicant for approval of the [section

505(b)(2)] application were conducted, or that claim a use for the listed or other drug." 21 C.F.R. § 314.54(a)(1)(vi). Put differently, FDA interprets the certification requirement as applicable to three classes of pioneer-drug patents: those for (1) a previously approved drug expressly "identif[ied]" in the application; (2) any "other" drugs previously approved by FDA, if the application relies upon such approval; and (3) any method-of-use for the "listed" and "other" drugs just mentioned.

In applying these rules, FDA has stated that a section "505(b)(2) application may rely on FDA's finding of safety and/or effectiveness for one *or more* listed drugs." 80 Fed. Reg. 6,802, 6,856 (2015) (proposed rule) (emphasis added) (describing this as FDA's "longstanding policy"). In addition, FDA has interpreted the concept of reliance expansively, requiring a section 505(b)(2) applicant to provide patent certifications for a pioneer drug if its application "seeks to rely *in any way* on" the pioneer drug's approval. *Fenofibrate Citizen Petition Response*, *supra*, at 7 (emphasis added). Thus, if an application "is based solely upon literature and does not rely expressly on an Agency finding of safety and effectiveness for a listed drug, the applicant must identify the listed drug(s)" discussed in the literature, "if there are any." *Draft Guidance*, *supra*, at 8.

Finally, FDA has directed section 505(b)(2) applicants to provide a certification when there is a particularly close relationship between a pioneer drug

and the proposed follow-on drug. In addition to any other drugs an applicant may choose to rely upon, the applicant must provide a certification regarding any "listed drug that is the pharmaceutical equivalent [of] the drug proposed in the 505(b)(2) application." *Fenofibrate Citizen Petition Response*, *supra*, at 9 (quoting *Draft Guidance*, *supra*, at 8); *see also* 80 Fed. Reg. at 6,856 (explaining that an applicant "implicitly reli[es]" on a pioneer drug's approval if the two drugs are pharmaceutically equivalent); 21 C.F.R. § 320.1(c) (defining "pharmaceutically equivalent"). When "no pharmaceutically equivalent drug product has previously been approved," FDA has admonished applicants to provide certifications for "the listed drug or drugs that are most similar to the drug for which approval is sought." *Fenofibrate Citizen Petition Response*, *supra*, at 10. This policy "help[s] ensure that the 505(b)(2) pathway is not used to circumvent the statutory obligation that would have applied if the proposed product was submitted as an ANDA—namely, submission of a patent certification." 80 Fed. Reg. at 6,856.

II. The District Court's Decision Undermines Hatch-Waxman's Grand Bargain.

The district court's interpretation of section 505(b)(2) threatens to undermine the interlocking system of benefits and burdens Congress built into the Hatch-Waxman Act. According to the district court, section 505(b)(2) applicants may reap the chief advantage provided by the Act—a shortcut to market that relies on pioneer drug approvals—without subjecting themselves to any of the

requirements intended to protect pioneer manufacturers. That construction of section 505(b)(2) is inconsistent with the Hatch-Waxman Act's structure and purpose, and with central aspects of FDA's regulatory guidance.

A. The District Court's Interpretation Of Section 505(b)(2) Disregards The Hatch-Waxman Act's Structure And Purpose.

The district court read the term "relied upon" in section 505(b)(2) narrowly, concluding that it is limited to the drug expressly "referenced" in the section 505(b)(2) application. Joint Appendix ("JA") 38, 75–77. The structure and purpose of the Hatch-Waxman Act point to a broader interpretation: A section 505(b)(2) application "relie[s] upon" FDA's approval of a pioneer drug if the finding of safety and efficacy for the pioneer drug is essential to approval of the follow-on drug.

Developing a pioneer drug is tremendously expensive. Today, the process generally takes 10 to 15 years from preclinical research through NDA approval and costs nearly $2.6 billion. Tufts Center for the Study of Drug Development, *Cost to Develop and Win Marketing Approval for a New Drug is $2.6 Billion* (Nov. 18, 2014), http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study. Pioneer manufacturers provide the resulting safety and effectiveness data to FDA with an expectation that the studies will be kept confidential. *See Omnitrope Citizen Petition Response*, *supra*, at 38.

Pioneers would have little incentive to conduct such costly and time-consuming research if FDA could turn around and use the data to approve competitors' section 505(b)(2) applications without regard to the statute's patent and regulatory-exclusivity protections. Under the district court's interpretation of section 505(b)(2), however, manufacturers could not bring pioneer drugs to market without making billions of dollars' worth of research available to competitors immediately and free of charge. Congress crafted Hatch-Waxman's grand bargain, and codified FDA's confidentiality policy, to avoid exactly this disincentive to innovation. "[I]t would frustrate Congress's intent to incentivize new drug development . . . if a second-in-time 505(b)(2) NDA could escape the reach of the" Act's regulatory-exclusivity and patent-certification provisions "by simply relying on a 505(b) NDA different than the first-in-time [pioneer] NDA." *Veloxis Pharm., Inc. v. FDA*, No. 14-2126, 2015 WL 3750672, at *9 (D.D.C. June 12, 2015).

The Hatch-Waxman Act's grand bargain thus requires a broader reading of the statutory phrase "relied upon"—one that encompasses any instance in which the safety and effectiveness findings for a pioneer manufacturer's NDA are essential to approval of a section 505(b)(2) application. Under this interpretation, follow-on manufacturers are able to piggyback on pioneer NDA approvals and thereby obtain a significant benefit, but only subject to the patent-certification and exclusivity protections designed to protect pioneer manufacturers' incentives. The

district court's interpretation, in contrast, permits section 505(b)(2) applicants to shirk their end of the grand bargain through artful drafting.

The district court perceived no reason why Congress would condition access to the "agency file drawer that contains scientific data pertinent to the evaluation of a new drug marketing application" on a section 505(b)(2) applicant's provision of a patent certification. JA63. But as explained above, the Hatch-Waxman Act is built on the premise that if the data contained in a pioneer NDA "were promptly made available to support applications for 'me-too' drugs . . . the incentive for private pharmaceutical research w[ould] be adversely affected." 39 Fed. Reg. at 44,634. In other words, Congress understood that there would *be* no "agency file drawer contain[ing] scientific data" unless pioneer manufacturers were given adequate assurance that the enormous investments necessary to generate the data would be protected.

The district court's interpretation of section 505(b)(2) would also undercut Congress's goal of allowing patent-infringement suits to "be resolved as quickly as possible." *TorPharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C. 2003). The Hatch-Waxman Act promotes this objective by requiring follow-on applicants to provide appropriate patent certifications and notice regarding the pioneer drugs they rely upon. If reliance is construed narrowly, to exclude instances in which an applicant fails to cite pioneer-drug approvals and counts on FDA to consider the

data supporting those approvals, then applicants will not have to certify to the pioneer manufacturer's patents. Consequently, pioneer NDA holders and patent owners will receive no notice when a potentially infringing follow-on drug is under FDA consideration—and thus no opportunity to use the pre-approval judicial-review procedures Congress built into the statute.[8]

B. The District Court's Decision Conflicts With FDA's Section 505(b)(2) Regulations And Guidance.

The district court's reasoning also conflicts with FDA policy in three important respects.

First, the district court incorrectly assumed that section 505(b)(2) applications necessarily rely upon one and only one pioneer drug: "the" reference listed drug. The district court asserted that section 505(b)(2) applicants "can rely on clinical studies that were previously submitted to FDA in support of another drug" and that "*[t]he* drug for which the borrowed studies were conducted is referred to as the 'Reference Listed Drug.'" JA28 (emphasis added). Similarly, the court stated that

[8] The district court's interpretation also raises a serious issue under the Fifth Amendment's Just Compensation Clause. Trade secrets are constitutionally-protected property, *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1002–04 (1984), and use of NDA data to support section 505(b)(2) applications would frustrate pioneer manufacturers' reasonable investment-backed expectation that FDA will use such data solely to approve the original NDA. Section 505(b)(2) should be interpreted to avoid this problem. *See Edward J. DeBartolo Corp. v. Fla. Gulf Coast Building & Constr. Trades Council*, 485 U.S. 568, 575 (1988).

> subsection (b)(2)(A) . . . unambiguously describe[s] two related types of patents that that require certification when an applicant files a Section 505(b)(2) application in reliance on another drug's safety and efficacy studies: patents that claim *the* reference listed drug and patents that claim a method of using *the* reference listed drug, so long as the applicant is seeking approval for that patented use.

JA83 (emphases added). The district court's consistent use of the phrase "the reference listed drug" indicates that the court viewed section 505(b)(2) applications as relying on one, and only one, listed drug. *See Rumsfeld v. Padilla*, 542 U.S. 426, 434 (2004) ("The consistent use of the definite article in reference to the custodian indicates that there is generally only one proper respondent."). That assumption is incorrect: FDA has explained that a section 505(b)(2) application "may rely on FDA's finding of safety and/or effectiveness for one *or more* listed drugs." 80 Fed. Reg., at 6,856 (emphasis added); *see also* 21 C.F.R. § 314.54(a)(1)(iv) (Section 505(b)(2) applications must include a certification "with respect to any relevant patents that claim the listed drug or that claim any other drugs on which investigations relied on by the applicant for approval of the application were conducted."). Thus, contrary to the district court's opinion, West-Ward's section 505(b)(2) application could have "relied on" FDA's approval of a second pioneer drug in addition to Col-Probenecid. *See* JA37–38.

Second, the district court incorrectly concluded that FDA policy "leave[s] it up to the" section 505(b)(2) applicant "to determine" which pioneer-drug approvals it will rely upon. JA71. While the statute and implementing regulations

grant applicants flexibility in determining the scope and content of a section 505(b)(2) application, that flexibility is not unlimited. As discussed above, a section 505(b)(2) application necessarily relies upon a pharmaceutically equivalent pioneer drug, whether or not the drug's approval is cited in the application. *See Fenofibrate Citizen Petition Response*, *supra*, at 9. Likewise, an applicant's decision not to cite a pioneer drug does not determine whether the application relies upon that pioneer drug's approval. *See id.* at 10; *see also Draft Guidance*, *supra*, at 8; 80 Fed. Reg. at 6,856 (section 505(b)(2) applicants sometimes "implicitly rel[y]" on a prior NDA approval). Instead, the reliance issue must be decided by evaluating the closeness of the follow-on and pioneer drugs and the applicant's reason for omitting the reference. *See Fenofibrate Citizen Petition Response*, *supra*, at 10–11 & n.15.

The district court rationalized its decision not to conduct this essential inquiry on the ground that FDA does not require section 505(b)(2) applicants to cite the "most appropriate" or "most similar" pioneer drugs. JA67. The district court's premise is questionable, given FDA's statement that "the 505(b)(2) applicant should choose the listed drug or drugs that are most similar to the drug for which approval is sought." *Fenofibrate Citizen Petition Response*, *supra*, at 9. But even if the district court is correct, there must be consequences that attach to the decision not to cite a closely-related drug—in particular, loss of ability to rely

on the findings of safety and efficacy for the omitted drug's NDA. The district court's interpretation, in contrast, allows section 505(b)(2) applicants to rely on FDA to fill in evidentiary gaps using data in its files, without regard to exclusivity periods and patent protections. Under this interpretation, section 505(b)(2) becomes a loophole that permits section 505(b)(2) applicants to undo Hatch-Waxman's grand bargain. Indeed, a section 505(b)(2) applicant in such a situation would be perversely incentivized to cite a less related drug in order to avoid confronting the most relevant patents in its certification obligations.

Third, the district court failed to observe the principle, firmly established in FDA precedent, that a section 505(b)(2) applicant may rely on the agency's finding that a pioneer drug is safe and effective, but not the data underlying that conclusion. The district court saw no problem with allowing FDA to consider "the previously-submitted safety and effectiveness data of third-party drug sponsors as part of its review of a Section 505(b)(2) application without securing the data owner's permission." JA58. According to the court, a pioneer manufacturer's "voluntary submission of its proprietary data to FDA waive[s] any right that applicant may have had to prohibit FDA from" using those data to assist other applicants "in the future." JA59. Neither of these assertions can be reconciled with FDA's longstanding policy that clinical studies and other raw data contained

in a pioneer NDA are confidential and may not be used by anyone other than the owner. *See Balancing Competition*, *supra*, at 275.

In short, the district court ignored the Hatch-Waxman Act's structure and purpose, as well as important aspects of FDA's regulatory framework. In so doing, the court upset the balance Congress and FDA have struck between innovation and open access.

CONCLUSION

The judgment of the district court should be reversed.

Respectfully submitted,

/s/ Robert A. Long

Robert A. Long
Krista H. Carver
Kevin King
COVINGTON & BURLING LLP
850 10th Street NW
Washington, DC 20001
(202) 662-6000

Attorneys for Amicus Curiae Pharmaceutical Research and Manufacturers of America

Dated: August 24, 2015

CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitations of Fed. R. App. P. 32(a)(7)(B) because this brief contains 6,909 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii) and D.C. Circuit Rule 32(a)(1).

2. 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 this brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 using 14-point Times New Roman font.

/s/ Robert A. Long

Robert A. Long
COVINGTON & BURLING LLP
850 10th Street NW
Washington, DC 20001
(202) 662-6000

Attorney for Amicus Curiae Pharmaceutical Research and Manufacturers of America

Dated: August 24, 2015

CERTIFICATE OF SERVICE

I hereby certify that on August 24, 2015, I caused the foregoing Brief of Amicus Curiae Pharmaceutical Research and Manufacturers of America to be electronically filed with the Clerk of the Court using the CM/ECF System, which will send notice of such filing to all parties that have entered an appearance in this action.

I further certify that, pursuant to D.C. Circuit Rules 25 and 31, I caused nine (9) paper copies of the foregoing Brief of Amicus Curiae Pharmaceutical Research and Manufacturers of America to be hand-delivered to the Clerk of the Court.

/s/ Robert A. Long

Robert A. Long
COVINGTON & BURLING LLP
850 10th Street NW
Washington, DC 20001
(202) 662-6000

Attorney for Amicus Curiae Pharmaceutical Research and Manufacturers of America

Dated: August 24, 2015