ORAL ARGUMENT NOT YET SCHEDULED
Nos. 15-5021 and 15-5022 (consolidated)

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

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

Plaintiffs-Appellants,

v.

SYLVIA MATHEWS BURWELL, in her official capacity as Secretary,
U.S. Department of Health and Human Services, and
MARGARET HAMBURG, M.D., in her official capacity as Commissioner of
Food and Drugs, Food and Drug Administration,

Defendants-Appellees.

HIKMA PHARMACEUTICALS PLC and
WEST-WARD PHARMACEUTICALS CORP.,

Intervenor-Defendants-Appellees.

On Appeal From The United States District Court For The District Of Columbia
Case Nos. 14-cv-1668 (KBJ) and 14-cv-1850 (KBJ)

REPLY BRIEF FOR APPELLANTS ELLIOTT ASSOCIATES, L.P., ELLIOTT INTERNATIONAL, L.P., AND KNOLLWOOD INVESTMENTS, L.P.

Matthew D. McGill
Lucas C. Townsend
GIBSON, DUNN & CRUTCHER LLP
1050 Connecticut Ave., N.W.
Washington, D.C. 20036
Telephone: (202) 955-8500

Michael A. Sitzman
Counsel of Record
GIBSON, DUNN & CRUTCHER LLP
555 Mission Street, Suite 3000
San Francisco, CA 94105
Telephone: (415) 393-8200
MSitzman@gibsondunn.com

Counsel for Elliott Appellants

UPDATED CERTIFICATE AS TO PARTIES

Plaintiffs-Appellants Elliott Associates, L.P., Elliott International, L.P., and Knollwood Investments, L.P. (together, the "Elliott Appellants") certify that the certificate in their opening brief is complete and correct, except that the Generic Pharmaceutical Association ("GPhA") has now appeared as *amicus curiae* in support of the Defendants-Appellees and Intervenor-Defendants-Appellees.

/s/ Michael A. Sitzman
Michael A. Sitzman

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

* Authorities upon which we chiefly rely are marked with an asterisk.

TABLE OF AUTHORITIES
(continued)

Page(s)

Statutes

Regulations

Other Authorities

* Authorities upon which we chiefly rely are marked with an asterisk.

GLOSSARY

ANDA	Abbreviated New Drug Application
FDA	Food and Drug Administration
FDCA	Food, Drug, and Cosmetic Act
GPhA	Generic Pharmaceutical Association
NDA	New Drug Application
RLD	Reference-Listed Drug

SUMMARY OF ARGUMENT

FDA approved Hikma's 505(b)(2) application for "Mitigare" (colchicine) for the prophylaxis of gout flares without requiring Hikma to certify to Takeda's Orange Book-listed patents covering the same use of the same drug—colchicine for the prophylaxis of gout flares. Despite clear overlap between Takeda's use patents and Hikma's drug product, FDA and Hikma insist that the binding regulation and governing statute did not require patent certification because Hikma relied upon a Reference-Listed Drug ("RLD") that was not Takeda's product, Colcrys®. The regulation and statute, however, do not make that exception or limit the certification requirement to the RLD. In fact, the RLD is not even mentioned in the binding regulation that FDA ignored.

Rather than focusing on the express language of FDA's binding regulation, appellees contend that colchicine has been used to treat gout for "centuries" (FDA Br. 6-7; Hikma Br. 8, 10; GPhA Br. 2), and that appellants' true motivation is to eliminate legitimate competitors from the market. FDA, Hikma, and their *amicus* GPhA implore the Court to disregard the clear text of Section 505(b)(2) of the FDCA and FDA's regulation at 21 C.F.R. § 314.50(i)(1)(iii)(B) interpreting the statute, in order to prevent Takeda and the Elliott Appellants from realizing a supposed "windfall" if FDA's unlawful approval of Mitigare is set aside. FDA Br. 26; Hikma Br. 40; GPhA Br. 6, 18.

Aside from being irrelevant, this revisionist history is inaccurate and incomplete. FDA itself found that prior to the groundbreaking dosing methodology that Mutual (later Takeda) developed with the invention of Colcrys®, 169 deaths were associated with the use of oral colchicine. JA127. And it was *FDA* that took the extraordinary step of removing all generic colchicine products from the market, deeming them unsafe, after FDA approved Colcrys®. FDA was "particular[ly] concern[ed]" that the generic drugs presented an unacceptable risk of potentially lethal drug-drug interactions—a problem solved by Colcrys®. JA36-37.

The life-saving advances made through the development of Colcrys® required Mutual to "conduct[] extensive research" and invest significant resources to obtain FDA approval. Takeda Br. 7-10. In recognition of this innovation, the U.S. Patent & Trademark Office issued Mutual seventeen patents, including the four Colcrys® use patents involved in this case.

FDA and Hikma seek to deprive Takeda and the Elliott Appellants of those intellectual property rights—the incentives that spur innovations like Colcrys®—by permitting Hikma to market Mitigare (a drug that began as a duplicate of Colcrys® and differs now only in its dosage form) without certifying to the Colcrys® use patents. Neither FDA's regulations implementing Section 505(b)(2) nor the statute itself allows this.

1. FDA's binding interpretation of Section 505(b)(2)(A) at 21 C.F.R. § 314.50(i)(1)(iii)(B) clearly required Hikma to certify to the Colcrys® use patents. FDA and Hikma seek to nullify that provision by arguing that it requires only the same certifications already required by 21 C.F.R. § 314.50(i)(1)(i)(A). That interpretation contradicts paragraph (i)(1)(iii)(B)'s text and this Court's precedents refusing to adopt interpretations that unnecessarily render regulatory provisions meaningless.

2. FDA's approval of Mitigare *separately* violated the plain text of Section 505(b)(2)(A). FDA twists the statute and contradicts its own regulations (and its litigating position before the district court) by arguing that "drug" must mean only drug product and not drug substance in Section 505(b)(2). Hikma, in contrast, interprets "drug" so restrictively that according to Hikma's interpretation, Section 505(b)(2) authorizes only applications for an RLD, not the applicant's own drug. The interpretations proffered by FDA and Hikma also effectively read the words "for which the applicant is seeking approval under this subsection" out of Section 505(b)(2)(A) and render Section 505(b)(2)(B) completely redundant. Only the Elliott Appellants offer an interpretation of the statute that gives meaning to all its parts.

FDA and Hikma also argue that FDA is entitled to *Chevron* deference, but FDA's only reasoned interpretation of the statute is in its binding regulation.

FDA's shifting interpretation of the statute in this litigation contradicts the regulation and is entitled to no deference.

3. Finally, to prop up their flawed interpretations, FDA and Hikma distort the careful balancing of interests that Congress performed in the Hatch-Waxman amendments to the FDCA. But 505(b)(2) applicants are not free to avoid the FDCA's patent-certification requirements by purporting to rely on unpatented RLDs like Col-Probenecid. That result would perversely deny innovators like Takeda the opportunity Congress provided to defend their intellectual property rights before infringing drugs flood the market. As the *amici* involvement in this case shows, the industry is closely following this test case; a decision for FDA would blaze a trail for generic manufacturers to circumvent innovators' patents.[1]

ARGUMENT

I. FDA's Approval Of Mitigare Was Arbitrary, Capricious, And Contrary To Law Because FDA's Binding Regulation Required Hikma To Certify To The Colcrys® Use Patents

FDA's binding regulation at 21 C.F.R. § 314.50(i)(1)(iii)(B) is clear, unambiguous, and fatal to FDA's unlawful approval of Mitigare. It provides: "If the labeling of the drug product for which the applicant is seeking approval includes an indication that, according to the [Orange Book] or in the opinion of the applicant,

[1] The text of the relevant statute and regulation is set out in the Addendum to this brief.

is claimed by a use patent, the applicant shall submit an applicable certification under paragraph (i)(1)(i) of this section." 21 C.F.R. § 314.50(i)(1)(iii)(B). The label for Mitigare (colchicine) included only one indication: "prophylaxis of gout flares." JA625. "[A]ccording to the [Orange Book]," that indication is "claimed by" Takeda's "use patent[s]" for Colcrys®. 21 C.F.R. § 314.50(i)(1)(iii)(B). Hikma did not "submit" any "certification" to the Colcrys® use patents, yet FDA nonetheless approved Hikma's Mitigare application.

Not a word of the above is disputed by either FDA or Hikma (or, for that matter, GPhA), and that is enough for this Court to set aside FDA's approval of Mitigare as arbitrary, capricious, and contrary to law. *See Nat'l Envtl. Dev. Ass'n's Clean Air Project v. EPA*, 752 F.3d 999, 1009 (D.C. Cir. 2014) ("[A]gency action may be set aside as arbitrary and capricious if the agency fails to comply with its own regulations.") (internal quotation omitted). FDA and Hikma do their best to elide this clear violation of FDA's regulations, burying it in the back of their briefs and treating it as merely part of the analysis regarding whether FDA's flawed interpretation of Section 505(b)(2) is entitled to *Chevron* deference. FDA Br. 37-39; Hikma Br. 27-30. The Court should not be fooled: Though FDA's binding regulation *also* demonstrates why FDA's *post hoc* interpretation of Section 505(b)(2) in this case is entitled to no deference, as described *infra*, the regulatory

violation is a sufficient and straightforward ground for the Court to dispose of this case.

Neither FDA nor Hikma defends the district court's clearly erroneous conclusion that 21 C.F.R. § 314.50(i)(1)(iii) merely "concerns proper labeling." JA84-85 n.25; *see* Elliott Br. 18 n.3. Instead, they argue that 21 C.F.R. § 314.50(i)(1)(iii)(B) requires certifications only where a separate subsection, § 314.50(i)(1)(i)(A), *also* requires certification to those patents. FDA Br. 39; Hikma Br. 28-29. But that interpretation cannot be squared with the regulation's text: the two provisions are complementary and use different language to delineate two distinct requirements. Paragraph (i)(1)(i)(A) requires certifications to "*each patent … that … claims a drug* (the drug product or drug substance that is a component of the drug product) *on which investigations that are relied upon by the applicant … were conducted* ***or that claims an approved use for such drug***." 21 C.F.R. § 314.50(i)(1)(i)(A) (emphases added). Paragraph (i)(1)(iii)(B), by comparison, requires a certification "[***i***]***f the labeling*** of" the applicant's drug product "***includes an indication that***, according to [the Orange Book] or in the opinion of the applicant, ***is claimed by a use patent***." 21 C.F.R. § 314.50(i)(1)(iii)(B) (emphases added). Paragraph (i)(1)(iii)(B) does not even obliquely refer to paragraph (i)(1)(i)(A) or mirror its language when establishing the circumstance under which a certification is required; rather, it directs the applicant to paragraph (i)(1)(i) only

for the purpose of choosing which "certification" listed under that paragraph should be made. *Id.*

Both Hikma and FDA advance untenable arguments that attempt to read into paragraph (i)(1)(iii)(B) a reference to the RLD found nowhere in that provision. Hikma's assertion that the "regulations" link patent certifications "to the listed drug 'relied upon by the applicant for approval'" (Hikma Br. 28-29 (quoting 21 C.F.R. § 314.50(i)(1)(i))) impermissibly conflates two regulatory provisions in an attempt to change the plain meaning of paragraph (i)(1)(iii)(B).

FDA's argument is no better. FDA posits that paragraph (i)(1)(iii)(B) addresses the possibility that an applicant may rely on an RLD "without seeking approval to market its product for all the same uses." FDA Br. 38. But that again is untethered from the text of paragraph (i)(1)(iii)(B), which *never* mentions the RLD. If FDA wishes to revise its binding regulations, it must do so through notice and comment, not an appellate brief. *See Nat'l Envtl. Dev.*, 752 F.3d at 1009.

Paragraph (i)(1)(iii)(B) does not rest its certification requirement on whether the conditions in (i)(1)(i) are met; rather it concisely provides that if the 505(b)(2) applicant's drug product has labeling that "includes an indication that, according to [the Orange Book] or in the opinion of the applicant, is claimed by a use patent," the applicant must certify to that patent. 21 C.F.R. § 314.50(i)(1)(iii)(B). Paragraph (i)(1)(i)(A) likewise does not rest its certification requirement on whether the

condition in (i)(1)(iii)(B) is met; rather, it requires "a certification with respect to *each patent*" that claims the RLD product or substance "or that claims an approved use for [the RLD product or substance]." *Id.* § 314.50(i)(1)(i)(A) (emphasis added).

FDA appears to argue as well that the only "applicable" certifications under paragraph (i)(1)(iii)(B) are to use patents for the RLD. *See* FDA Br. 38-39. But as the Elliott Appellants have explained (Elliott Br. 18-20), the word "applicable" cannot bear the weight FDA attributes to it, for several reasons.

First, the plain meaning of "applicable certification under paragraph (i)(1)(i)" in this context is that once it is established (as explained above) that the applicant's label overlaps with "a use patent," the applicant "shall submit" a certification under paragraph (i)(1)(iii)(B). Which certification? The one describing the circumstance—one of four possibilities listed in "paragraph (i)(1)(i)"—"applicable" to the applicant's situation.

Second, FDA's interpretation of "applicable"—that a certification under paragraph (i)(1)(iii)(B) is required only where the conditions for certification in paragraph (i)(1)(i)(A) are met—renders paragraph (i)(1)(iii)(B) a nullity. An applicant would never need to consult paragraph (i)(1)(iii)(B) to determine its certification obligations.

Third, interpreting "applicable" to permit an applicant not to certify to a use patent because the use patent is not for the RLD reads the *mandatory* certification requirement out of the regulation. 21 C.F.R. § 314.50(i)(1)(iii)(B) ("the applicant *shall submit* an applicable certification") (emphasis added). After meeting the requirements of the regulation, the only question remaining is *which* "applicable" certification will be submitted. This Court does not accept agency interpretations that unnecessarily render words or clauses in regulations, let alone entire sections, "surplusage." *Sierra Club v. EPA*, 536 F.3d 673, 680 (D.C. Cir. 2008) ("As the Supreme Court has instructed, it is [a court's] duty to give effect, if possible, to every clause and word of a statute … . The same is true for regulations.") (internal quotation omitted).

The Elliott Appellants offer this Court the *only* interpretation of 21 C.F.R. § 314.50(i)(1)(iii)(B) that gives it any effect. FDA claims that "this regulation serves to 'reinforce'" (read: duplicate) "the 'relationship between reliance and certification'" that exists in paragraph (i)(1)(i)(A). FDA Br. 39 (quoting JA646[2]).

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[2] The source FDA quotes at JA646 is a 2004 FDA response to a Citizens Petition by Abbott Laboratories. That FDA response did not discuss 21 C.F.R. § 314.50(i)(1)(iii)(B). If FDA means to imply that the 2004 response established that paragraph (i)(1)(iii)(B) serves only to "reinforce" the certification required under paragraph (i)(1)(i), FDA is wrong. In any event, FDA's supposed "long-standing view" of what Section 505(b)(2) requires, expressed in responses to Citizens Petitions (FDA Br. 38), cannot overrule its binding regulation, and FDA does not argue otherwise. *See Nat'l Envtl. Dev.*, 752 F.3d at 1009.

But paragraph (i)(1)(i)(A) is clear; it needs no "reinforcement" through repetition in another section. *See Nat'l Ass'n of Home Builders v. Defenders of Wildlife*, 551 U.S. 644, 669 (2007) ("[W]e have cautioned against reading a text in a way that makes part of it redundant."); *accord*, *e.g.*, *Solis v. Summit Contractors, Inc.*, 558 F.3d 815, 823-24 (8th Cir. 2009) (collecting cases). Try as they might, FDA and Hikma cannot erase that provision from FDA's binding regulations and cannot import words and limitations that do not exist. Hikma did not file the required certification to the Colcrys® use patents, and FDA's approval of Mitigare must be set aside as arbitrary and capricious.[3]

II. FDA's Approval Of Mitigare Was Independently Arbitrary, Capricious, And Contrary To Law Because Section 505(b)(2) Required Hikma To Certify To The Colcrys® Use Patents

FDA's approval of Mitigare also violated Section 505(b)(2) of the FDCA, which required Hikma to certify to "*each patent* … which claims a use for *such drug for which the applicant is seeking approval under this subsection*." 21 U.S.C. § 355(b)(2)(A) (emphases added). FDA admits, as it must, that "FDA may not approve an application that lacks a required certification." FDA Br. 5. Neither FDA nor Hikma presents any persuasive argument regarding how FDA could excuse

[3] FDA incorrectly suggests that the certification issue might become "moot" if Takeda's patent infringement complaint is dismissed (FDA Br. 37 n.2), ignoring that FDA *may not approve* an application that lacks a required certification (*id.* at 5; 21 U.S.C. § 355(d)(6)).

Hikma's failure to certify to "each patent" claiming a use for colchicine, the drug "for which [Hikma was] seeking approval."

A. The Elliott Appellants Offer The Only Sensible Interpretation Of Section 505(b)(2)'s Unambiguous Text

Section 505(b)(2) inherently refers to two different "drugs"—the applicant's drug and the reference drug (the RLD). Only the Elliott Appellants' interpretation accounts for this incontrovertible fact.

FDA argues that the word "drug" always means "drug product, not active ingredient" in Section 505(b)(2). FDA Br. 35 (internal quotation omitted). But FDA never specifies *which* drug product—the applicant's product (Mitigare) or the RLD (Col-Probenecid). FDA studiously avoids committing to one or the other throughout the provision, because doing so would render the statute inoperable. Thus, the "repetition" of the word "drug" in the statute does not "'strongly suggest[]' that Congress intended 'drug' to have a consistent meaning," as FDA asserts. *Id.* (quoting JA78); *see also* Hikma Br. 24 (quoting *Powerex Corp. v. Reliant Energy Servs., Inc.*, 551 U.S. 224, 232 (2007); *Brown v. Gardner*, 513 U.S. 115, 118 (1994)). To the contrary, "the natural presumption that identical words used in different parts of the same act are intended to have the same meaning … is not rigid and readily yields whenever there is such variation in the connection in which the words are used as reasonably to warrant the conclusion that they were employed in different parts of the act with different intent." *Envtl. Defense v. Duke*

Energy Corp., 549 U.S. 561, 574 (2007) (internal quotation omitted). In other words: "Context counts." *Id.* at 576; *see also NetCoalition v. SEC*, 715 F.3d 342, 350 (D.C. Cir. 2013); *Ne. Hosp. Corp. v. Sebelius*, 657 F.3d 1, 11 (D.C. Cir. 2011). By equating "drug" with "drug product" and requiring strict consistency throughout the statute, FDA has rendered Section 505(b)(2) inoperative—"drug" *must* refer to two different drugs.

Consistency is not a virtue of FDA's statutory interpretation in any event. FDA's own regulations *interpreting Section 505(b)(2)* expressly recognize that "drug" can mean *either* "the drug product or the drug substance that is a component of the drug product." 21 C.F.R. § 314.50(i)(1)(i)(A); *see also* Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,339 (Oct. 3, 1994) (FDA "on its own initiative" inserted that language "to clarify the types of patents for which a certification should be made"). Indeed, FDA *admitted* in the district court that under its interpretation of the statute, the word "drug" in the first clause of Section 505(b)(2)(A) must mean "the drug product or drug substance that is a component of the drug product," while later in the *same sentence* "such drug" would refer only to patents claiming a use of "the product," not of the substance. Doc. #62, at 3-4.[4]

[4] FDA's contention that the Elliott Appellants "forfeited" this argument "by failing to raise it below" (FDA Br. 36 n.1) is belied by the record. Paragraph

FDA now implausibly asserts that it "has interpreted the word 'drug' in 21 U.S.C. § 355(b)(2) to refer to *drug product*, not *active ingredient*," apparently across the board. FDA Br. 35 (internal quotation omitted). If FDA is attempting to retreat from its previous position in this case (which is also enshrined in its regulation) *sub silentio*, that approach to statutory interpretation lacks credibility. Whatever the reason, FDA is wrong: "drug" can mean "drug product" or "drug substance" in Section 505(b)(2), depending upon its context. Contrary to appellees' arguments, the only sensible interpretation of "drug" in the latter part of Section 505(b)(2)(A) is that an applicant must certify to "each patent" claiming "a use for" the drug product or drug substance "for which the applicant is seeking approval."

Hikma's interpretation of "drug," on the other hand, clings to consistency even at the expense of coherence. According to Hikma's diagram, the word "drug" in Section 505(b)(2) *always* means the RLD. *See* Hikma Br. 22-23. Hikma reads the beginning of Section 505(b)(2) as such: "An application submitted under paragraph (1) for ***a drug*** for which the investigations described in clause (A) of such

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(i)(1)(i)—the provision containing the interpretation of "drug" that FDA seeks to escape—has been a key part of the briefing since the Elliott Appellants' memorandum in support of their motion for summary judgment. Doc. #14-1, at 26, 36 (Elliott Appellants' motion for summary judgment); Doc. #62, at 3 (FDA's opposition); Doc. #64, at 15-16 (Elliott Appellants' reply). In any event, FDA's erroneous forfeiture assertion, raised only in a perfunctory footnote, is itself forfeited. *See Hutchins v. District of Columbia*, 188 F.3d 531, 539 n.3 (1999) (en banc).

paragraph and ***relied upon by the applicant*** … were not conducted by or for the applicant." 21 U.S.C. § 355(b)(2) (emphases in Hikma Br. 22). That is completely untenable. The quoted language must refer to *Hikma's drug* (Mitigare or colchicine), not the RLD, because Hikma did not submit an application for Col-Probenecid. "Drug" cannot be interpreted the same way throughout the statute; otherwise, Hikma would be precluded from seeking approval of Mitigare (colchicine), while relying on the investigations of a different drug, Col-Probenecid. Again, only the Elliott Appellants' interpretation accounts for this reality.

Congress meticulously used the words surrounding each use of "drug" in Section 505(b)(2) to distinguish when it meant a ***drug product***—"an application submitted … for a drug" (Mitigare, *see* 21 U.S.C. § 355(b)(2)), and a patent that "claims the drug for which [the] investigations [described in clause (A)] were conducted" (Col-Probenecid, *see id.* § 355(b)(2)(A))—from when it meant a ***drug substance***—"such drug for which the applicant is seeking approval under this subsection" (colchicine). *Id.* As explained in the Elliott Appellants' opening brief, the adjectival phrase "for which the applicant is seeking approval under this subsection" naturally modifies "drug," the word to which it is adjacent. *See* Elliott Br. 25-26.

FDA's response regarding the operation of the "for which" phrase is utter silence. Indeed, when attempting to explain why "such drug" means the RLD rather

than colchicine, FDA manufactures its preferred reading of the statute by simply omitting the "for which" phrase. *See* FDA Br. 35. If that was Congress's intent, it would have been much simpler to end the provision after "such drug." It is thus quite ironic for FDA to accuse the Elliott Appellants of ignoring "such" in the statute. *Id.* at 36. And, of course, they do not. The word "such" works in conjunction with the phrase "for which the applicant is seeking approval" to refer to colchicine—the drug that was the subject of Hikma's application.

Hikma, meanwhile, would interpret the "for which" phrase to modify "the entire term 'a use for such drug.'" Hikma Br. 25. Thus, together with Hikma's interpretation of "drug" above, Hikma would read the statutory text to require certification to "each patent" claiming a "use for [Col-Probenecid]" for which the applicant seeks approval. But Hikma obviously was not seeking approval for a "use for [Col-Probenecid]"—it was seeking approval for a use of *colchicine*. Hikma's erroneous interpretation once again illuminates that the only sensible interpretation of "such drug for which the applicant is seeking approval" is the drug substance, colchicine. And it remains completely undisputed in this case that the Colcrys® use patents claimed the *exact same* "use for [colchicine] for which [Hikma] [wa]s seeking approval." 21 U.S.C. § 355(b)(2)(A).

Finally, FDA and Hikma struggle in vain to explain what meaningful role Section 505(b)(2)(B) could possibly play under their interpretations of the statute.

See FDA Br. 36; Hikma Br. 25-26. According to appellees, Sections 505(b)(2)(A) and 505(b)(2)(B) are entirely redundant: To satisfy Section 505(b)(2)(A), the applicant would research which use patents for the RLD overlap with the use for which the applicant is seeking approval. For the use patents that overlap, the applicant must file a certification. 21 U.S.C. § 355(b)(2)(A). For those that do not, no certification is required. Then, to satisfy Section 505(b)(2)(B), the applicant apparently would undertake the same inquiry. For the use patents that overlap, no carve-out statement is required; for the use patents that do not overlap, the applicant must file a carve-out statement. *Id.* § 355(b)(2)(B). There is no reason to adopt an interpretation of the statute under which two adjacent provisions accomplish the same end when a more sensible interpretation is available. *See*, *e.g.*, *Haase v. Sessions*, 893 F.2d 370, 373 n.5 (D.C. Cir. 1990) ("[I]t is a well-settled principle of statutory construction that all words in a statute are to be assigned meaning and not to be construed as duplicative or surplusage."); *accord Williams v. Taylor*, 529 U.S. 362, 404 (2000).

The Elliott Appellants' interpretation of Section 505(b)(2)(A) maintains a role for both that provision and 505(b)(2)(B): The former requires the applicant to certify to patents claiming the RLD "or … a use for such drug for which the applicant is seeking approval"—a use for colchicine. 21 U.S.C. § 355(b)(2)(A). The latter requires the applicant to file a carve-out statement if a use patent for the RLD

"does not claim a use for which the applicant is seeking approval." *Id.* § 355(b)(2)(B). Here, for example, if Col-Probenecid *had* any use patents (it did not), Hikma would have filed a certification to the Colcrys® use patents under Section 505(b)(2)(A) and a carve-out statement for the Col-Probenecid use patents under Section 505(b)(2)(B).

FDA has essentially no answer for the legislative history that confirms that Section 505(b)(2)(B) requires certification to "*all use patents* which claim an indication *for the drug for which the applicant is seeking approval*." H.R. Rep. No. 98-857, pt. 1, at 32 (emphases added). Hikma, on the other hand, argues that this report "merely replaces the word 'use' from Section 505(b)(2)(A) with the word 'indication.'" Hikma Br. 26. Hikma is wrong. The Committee Report language also uses the word "the" (rather than "such") before the word "drug" when discussing relevant use patents. The Report thus confirms that, as explained above, Congress did not use "such drug" in Section 505(b)(2)(A) to refer to the RLD, but in conjunction with the "for which" phrase to refer to "the/such drug for which the applicant is seeking approval"—here, colchicine.

B. FDA's Binding Regulation Is Its Only Interpretation Of Section 505(b)(2) Entitled To *Chevron* Deference

FDA and Hikma argue in the alternative that the Court should defer to FDA's interpretation of Section 505(b)(2)(A). FDA Br. 37-38; Hikma Br. 27-30. Neither of them disputes that an interpretation that is contrary to FDA's binding

interpretation in 21 C.F.R. § 314.50(i)(1)(iii)(B) is not entitled to deference. Rather, as discussed in Part I, *supra*, they distort that regulation in order to avoid its impact on this case. For the reasons discussed above, the Court should hold that FDA is bound by its regulation: a 505(b)(2) applicant must file an applicable certification whenever the applicant's label "includes an indication that … is claimed by a use patent." 21 C.F.R. § 314.50(i)(1)(iii)(B). Moreover, the only source FDA cites for its supposedly "long-held" interpretation of the statute is a 2004 Citizens Petition response that addressed a different issue and did not grapple with the import of Section 314.50(i)(1)(iii)(B).

FDA's approach to the issue of *Chevron* deference erases any notion that its interpretation of Section 505(b)(2) is anything more than a *post hoc* litigation position. In the district court, FDA's *lead argument* was that "the Term 'Such Drug' is Ambiguous." Doc. #62, at 7; *see also id.* ("Despite the ambiguity of the word 'drug' in section 505(b)(2)(A), Elliott nonetheless contends that this is a Chevron step 1 case."). Indeed, FDA cited its own regulation stating that "drug" could mean "drug product" or "drug substance" in support of its argument that the statute was ambiguous. *See supra* n.4. Yet FDA now argues that Section 505(b)(2) is unambiguously in its favor, and it argues only in the alternative for deference under *Chevron*'s second step. FDA Br. 37 ("Even if the statute were ambiguous in this regard, this Court should defer" to FDA's interpretation.). FDA does not ex-

plain—or even acknowledge—yet another shift in its position. In short, FDA's "flip-flops" and "several *different* positions" are "the sort of '*post hoc* rationalizations' to which courts will not defer." *Akzo Nobel Salt, Inc. v. Fed. Mine Safety & Health Rev. Comm'n*, 212 F.3d 1301, 1304-05 (D.C. Cir. 2000).

III. FDA And Hikma Distort The *Quid Pro Quo* Under Hatch-Waxman Between Innovators And Manufacturers Who Submit 505(b)(2) Applications

Finally, throughout their briefs, FDA and Hikma prop up their erroneous interpretations of FDA's regulation and Section 505(b)(2) by appealing to a fictitious narrative regarding the abbreviated approval pathways created by the Hatch-Waxman Act. Prior to Hatch-Waxman, manufacturers seeking approval to market a lower-cost alternative to a brand-name drug had few, if any options. They could either conduct the expensive and time-consuming trials necessary to gain FDA approval of a new drug, or submit a "paper NDA" attempting to prove their drug's safety by reference to "learned articles" demonstrating the safety of the chemical compound. *See* Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 Food & Drug L.J. 187, 187 (1999). Moreover, even the unlicensed testing of patented brand-name drugs could expose manufacturers to liability for infringement under the Patent Act, thus effectively preventing generic drug companies from even beginning to develop a com-

peting drug product until all patent coverage for the pioneer drug had expired. *See Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858, 863-64 (Fed. Cir. 1984).

The Hatch-Waxman Act aimed to incentivize the speedy entry of lower-cost drug products while balancing the need to reward the substantial investments required for discovering and developing new drugs. *See* Elliott Br. 7-8 (citing cases describing the balance struck). Among the methods for achieving these goals, the Hatch-Waxman Act required brand-name manufacturers to identify any relevant patent information, which FDA publishes in the Orange Book, "[t]o facilitate the approval of generic drugs as soon as patents allow." *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1676 (2012).

But publication of brand-name manufacturers' patent information is only half the statutory balance. On the other side of the ledger, Congress required applicants filing ANDAs and 505(b)(2) applications to certify to relevant patents listed in the Orange Book, since FDA "cannot authorize a generic drug that would infringe a patent." *Id.* Because Hikma took advantage of the 505(b)(2) shortcut and sought approval for a method of use of colchicine that was already claimed by Takeda's patents listed in the Orange Book, Hikma was required to file a patent certification with respect to the Colcrys® use patents.

In a *post-hoc* effort to justify their actions, FDA, Hikma, and GPhA reinterpret this history and attempt to restrike the balance that Congress struck. *See* FDA

Br. 37; Hikma Br. 22, 27; GPhA Br. 15-16. In their view, innovators as a class receive absolutely nothing from the Hatch-Waxman process for 505(b)(2) applications, even though that process requires innovators to provide their patent information to FDA and permit would-be generics to utilize the teachings of their patents before expiry. Whereas ANDA applicants must certify to the patents of the drug they wish to duplicate, 505(b)(2) applicants get to choose, in their sole discretion, to which patents (if any) they will certify by selecting any RLD among those in the Orange Book.

As the facts of this case demonstrate, 505(b)(2) applicants in such a slanted system could run roughshod over the interests of innovators. Hikma initially submitted a 505(b)(2) application for a duplicate of Colcrys® and did not certify to the Colcrys® use patents, and Mutual (later Takeda) had to file a Citizens Petition to prevent Hikma from circumventing the ANDA pathway. *See* JA472-73; JA483. Rather than file an ANDA and certify to the Colcrys® use patents, Hikma changed the form of its 0.6-milligram colchicine drug from tablet to capsule, chose an unpatented combination drug (Col-Probenecid) with different active ingredients, concentrations, dosage form, and indications as the RLD, and once again did not certify to the Colcrys® use patents.

Under FDA's novel and distorted view of Section 505(b)(2), that dissimulation is to be applauded and encouraged. Thankfully, neither Section 505(b)(2) nor

FDA's binding regulation permit it. This Court should not allow FDA to rewrite the Hatch-Waxman bargain in Hikma's favor.

CONCLUSION

For the foregoing reasons, the Court should reverse the decision below by holding unlawful and setting aside FDA's approval of Mitigare.

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Respectfully submitted,

/s/ Michael A. Sitzman

Michael A. Sitzman
GIBSON, DUNN & CRUTCHER LLP
555 Mission Street, Suite 3000
San Francisco, CA 94105
Telephone: (415) 393-8200
Facsimile: (415) 393-8306
MSitzman@gibsondunn.com

Matthew D. McGill
Lucas C. Townsend
GIBSON, DUNN & CRUTCHER LLP
1050 Connecticut Ave., N.W.
Washington, D.C. 20036
Telephone: (202) 955-8500
Facsimile: (202) 530-9662

Counsel for Elliott Appellants

CERTIFICATE OF COMPLIANCE
WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS

1. This brief complies with the type-volume requirement of Federal Rule of Appellate Procedure 32(a)(7), as well as this Court's per curiam Order dated July 1, 2015, because this brief contains 4,994 words, as determined by the word-count function of Microsoft Word 2003, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii); and

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6) because this brief has been prepared in a proportionally spaced typeface using Microsoft Word 2003 in 14-point Times New Roman font.

/s/ Michael A. Sitzman
GIBSON, DUNN & CRUTCHER LLP
555 Mission Street, Suite 3000
San Francisco, CA 94105
(415) 393-8200

Addendum

TABLE OF CONTENTS

21 U.S.C. § 355

§ 355 New Drugs.

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 355c of this title. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include—

(A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section—

(i) that such patent information has not been filed,

(ii) that such patent has expired,

(iii) of the date on which such patent will expire, or

(iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

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

* * *

21 C.F.R. § 314.50

§ 314.50 Content and format of an application.

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

* * *

(h) *Patent information.* The application is required to contain the patent information described under § 314.53.

(i) *Patent certification* —(1) *Contents.* A 505(b)(2) application is required to contain the following:

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

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

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

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

(*4*) That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. The applicant shall entitle such a certification "Paragraph IV Certification". This certification shall be submitted in the following form:

I, (*NAME OF APPLICANT*), CERTIFY THAT PATENT NO. _____ (*IS INVALID, UNENFORCEABLE, OR WILL NOT BE INFRINGED BY THE MANUFACTURE, USE, OR SALE OF*) (*NAME OF PROPOSED DRUG PRODUCT*) FOR WHICH THIS APPLICATION IS SUBMITTED.

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

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

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

IN THE OPINION AND TO THE BEST KNOWLEDGE OF (*NAME OF APPLICANT*), THERE ARE NO PATENTS THAT CLAIM THE DRUG OR DRUGS ON WHICH INVESTIGATIONS THAT ARE RELIED UPON IN THIS APPLICATION WERE CONDUCTED OR THAT CLAIM A USE OF SUCH DRUG OR DRUGS.

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

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

(2) *Method of manufacturing patent.* An applicant is not required to make a certification with respect to any patent that claims only a method of manufacturing the drug product for which the applicant is seeking approval.

(3) *Licensing agreements.* If a 505(b)(2) application is for a drug or method of using a drug claimed by a patent and the applicant has a licensing agreement with the patent owner, the applicant shall submit a certification under paragraph (i)(1)(i)(A)(*4*) of this section ("Paragraph IV Certification") as to that patent and a statement that it has been granted a patent license. If the patent owner consents to an immediate effective date upon approval of the 505(b)(2) application, the application shall contain a written statement from the patent owner that it has a licensing agreement with the applicant and that it consents to an immediate effective date.

(4) *Late submission of patent information.* If a patent described in paragraph (i)(1)(i)(A) of this section is issued and the holder of the approved application for the patented drug does not submit the required information on the patent within 30 days of issuance of the patent, an applicant who submitted a 505(b)(2) application that, before the submission of the patent information, contained an appropriate patent certification is not required to submit an amended certification. An applicant whose 505(b)(2) application is filed after a late submission of patent information or whose 505(b)(2) application was previously filed but did not contain an appropriate patent certification at the time of the patent submission shall submit a certification under paragraph (i)(1)(i) or (i)(1)(ii) of this section or a statement under paragraph (i)(1)(iii) of this section as to that patent.

(5) *Disputed patent information.* If an applicant disputes the accuracy or relevance of patent information submitted to FDA, the applicant may seek a confirmation of the correctness of the patent information in accordance with the procedures under § 314.53(f). Unless the patent information is withdrawn or changed, the applicant must submit an appropriate certification for each relevant patent.

(6) *Amended certifications.* A certification submitted under paragraphs (i)(1)(i) through (i)(1)(iii) of this section may be amended at any time before the effective date of the approval of the application. An applicant shall submit an amended certification as an amendment to a pending application or by letter to an approved application. If an applicant with a pending application voluntarily makes a patent cer-

tification for an untimely filed patent, the applicant may withdraw the patent certification for the untimely filed patent. Once an amendment or letter for the change in certification has been submitted, the application will no longer be considered to be one containing the prior certification.

(i) *After finding of infringement.* An applicant who has submitted a certification under paragraph (i)(1)(i)(A)(*4*) of this section and is sued for patent infringement within 45 days of the receipt of notice sent under § 314.52 shall amend the certification if a final judgment in the action is entered finding the patent to be infringed unless the final judgment also finds the patent to be invalid. In the amended certification, the applicant shall certify under paragraph (i)(1)(i)(A)(*3*) of this section that the patent will expire on a specific date.

(ii) *After removal of a patent from the list.* If a patent is removed from the list, any applicant with a pending application (including a tentatively approved application with a delayed effective date) who has made a certification with respect to such patent shall amend its certification. The applicant shall certify under paragraph (i)(1)(ii) of this section that no patents described in paragraph (i)(1)(i) of this section claim the drug or, if other relevant patents claim the drug, shall amend the certification to refer only to those relevant patents. In the amendment, the applicant shall state the reason for the change in certification (that the patent is or has been removed from the list). A patent that is the subject of a lawsuit under § 314.107(c) shall not be removed from the list until FDA determines either that no delay in effective dates of approval is required under that section as a result of the lawsuit, that the patent has expired, or that any such period of delay in effective dates of approval is ended. An applicant shall submit an amended certification as an amendment to a pending application. Once an amendment for the change has been submitted, the application will no longer be considered to be one containing a certification under paragraph (i)(1)(i)(A)(*4*) of this section.

(iii) *Other amendments.* (A) Except as provided in paragraphs (i)(4) and (i)(6)(iii)(B) of this section, an applicant shall amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate.

(B) An applicant is not required to amend a submitted certification when information on an otherwise applicable patent is submitted after the effective date of approval for the 505(b)(2) application.

* * *

CERTIFICATE OF SERVICE

I hereby certify that on this 30th day of October, 2015, I caused the foregoing Reply Brief for Appellants Elliott Associates, L.P., Elliott International, L.P., and Knollwood Investments, L.P. to be electronically filed with the Clerk of the Court for the United States Court of Appeals for the District of Columbia Circuit using the appellate CM/ECF system. Service was accomplished on the following parties via the Court's CM/ECF system:

Sonia K. McNeil
Scott R. McIntosh
U.S. Department of Justice
Civil Division, Appellate Staff
950 Pennsylvania Avenue, N.W.
Washington, D.C. 20530-0001
sonia.k.mcneil@usdoj.gov
scott.mcintosh@usdoj.gov

Jessica R. Gunder
U.S. Department of Justice
Office of Consumer Litigation
Room 6400-South
450 Fifth Street, N.W.
Washington, D.C. 20001
jessica.r.gunder@usdoj.gov

Andrew E. Clark
U.S. Department of Justice
Consumer Protection Branch
P.O. Box 386
Washington, D.C. 20044-0386
andrew.clark@usdoj.gov

Counsel for Sylvia Mathews Burwell and Margaret Hamburg

Catherine E. Stetson
Jessica L. Ellsworth
Morgan L. Goodspeed
Hogan Lovells US LLP
Columbia Square
555 13th Street, N.W.
Washington, D.C. 20004-1109
cate.stetson@hoganlovells.com
jessica.ellsworth@hoganlovells.com
morgan.goodspeed@hoganlovells.com

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

Robert A. Long, Jr.
Kevin F. King
Covington & Burling LLP
One CityCenter
850 Tenth Street, N.W.
Washington, D.C. 20001-4956
rlong@cov.com
kking@cov.com

Counsel for Pharmaceutical Research and Manufacturers of America

Charles Bennett Klein
Jovial Wong
Ilan Wurman
Winston & Strawn LLP
1700 K Street, N.W.
Washington, D.C. 20006-3817
cklein@winston.com
JWong@winston.com
IWurman@winston.com

Samuel S. Park
Winston & Strawn LLP
35 West Wacker Drive
Chicago, IL 60601
spark@winston.com

Counsel for Hikma Pharmaceuticals PLC and West-Ward Pharmaceuticals Corp.

Carlos T. Angulo
Andrew N. Goldfarb
Zuckerman Spaeder LLP
1800 M Street, N.W.
Suite 1000
Washington, D.C. 20036-5802
cangulo@zuckerman.com
Agoldfarb@zuckerman.com

Counsel for Generic Pharmaceutical Association

/s/ Michael A. Sitzman
GIBSON, DUNN & CRUTCHER LLP
555 Mission Street, Suite 3000
San Francisco, CA 94105
(415) 393-8200