**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

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| BRAEBURN INC.,<br><br>Plaintiff,<br><br>v.<br><br>UNITED STATES FOOD AND DRUG ADMINISTRATION, et al.,<br><br>Defendants,<br><br>and<br><br>INDIVIOR INC.,<br><br>Intervenor-Defendant | Civil Action No. 19-982 (BAH)<br><br>Chief Judge Beryl A. Howell |

**MEMORANDUM OPINION**

Both the plaintiff, Braeburn Inc., and the intervenor-defendant, Indivior Inc., are pharmaceutical companies that manufacture drug products using buprenorphine, a safer alternative to methadone, to treat moderate-to-severe opioid use disorder ("OUD"). All parties recognize the serious national public health problem posed by OUD and the need for effective treatment options for patients with this addiction. Braeburn's product, Brixadi, delivers buprenorphine through an injectable depot that releases buprenorphine over either a weekly or monthly period. In July 2017, Braeburn applied to the Food & Drug Administration ("FDA") for approval of Brixadi and, on December 21, 2018, received tentative approval for both Brixadi Weekly and Monthly. The critical hitch prompting this lawsuit is that, while Brixadi Weekly could receive final approval once Braeburn submitted proposed labeling to the FDA, Brixadi Monthly was not eligible for final approval until November 30, 2020, upon expiration of a three-year right to exclusivity, under 21 U.S.C. § 355(c)(3)(E)(iii), belonging to Indivior's

buprenorphine drug product, Sublocade, which also is an injectable depot that releases buprenorphine over a one-month period.

Braeburn instituted this action on April 9, 2019 against the FDA and the Department of Health and Human Services, as well as the heads of those agencies in their official capacities, challenging the FDA's determination that Brixadi Monthly cannot be finally approved until Sublocade's three-year exclusivity expires. See generally, Compl., ECF No. 1. Shortly after, Indivior intervened as a defendant. Mot. Intervene, ECF No. 13; see also 1st Min. Order (Apr. 12, 2019) (granting Indivior's motion to intervene).

Now pending before the Court are cross-motions for summary judgment filed by Braeburn, ECF No. 24, Indivior, ECF No. 26, and the FDA, ECF No. 28. For the reasons explained below, Braeburn's motion is granted and both Indivior's motion and the FDA's motion are denied.[1]

## I. BACKGROUND

### A. Statutory and Regulatory Background

#### 1. New Drug Applications

Under the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 301 et seq., new drugs may not be introduced into interstate commerce without the FDA's approval. Id. § 355(a). To obtain FDA approval for a new drug, the drug's sponsor must file an application containing, inter alia, "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." Id. § 355(b)(1)(A). Originally, "all such applications were standalone applications: applications for which the drug's proponent

[1] Braeburn also filed a motion for preliminary injunction, see Mot. Prelim. Inj., ECF No. 7, which the parties agreed to table to move ahead with expedited cross-motions for summary judgment, see Joint Status Report (Apr. 12, 2019), ECF No. 17. Since this decision resolves the merits of Braeburn's action, the motion for a preliminary injunction is denied as moot.

either conducted, or secured a right to reference, all the investigations used to demonstrate the drug's safety and efficacy." Otsuka Pharm. Co. v. Price ("Otsuka II"), 869 F.3d 987, 989 (D.C. Cir. 2017).

That changed in 1984 when Congress passed the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98–417, 98 Stat. 1585 ("Hatch-Waxman Amendments"), amending the FDCA to introduce two streamlined paths for the sponsor of a new drug to seek FDA approval. The path utilized by the drugs at issue here, pursuant to § 505(b)(2) of the FDCA, as amended, allows a new-drug sponsor to rely 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) (codifying § 505(b)(2) of the FDCA), rather than conduct all its own investigations of the new drug's safety and effectiveness. Such an application must meet the remaining requirements codified in § 355(b)(1) and must certify that marketing the new drug would not infringe certain patent protections. Id. § 355(b)(2)(A). These applications may be "submitted for either a change to a previously approved drug or for an entirely new chemical entity, and, in some instances, may describe a drug product with substantial differences from a listed drug." Administrative Record ("AR") 412 (sealed).[2]

[2] The parties submitted a certified index of the administrative record, in accordance with Local Civil Rule 7(n), see Notice of Filing of Index of Administrative Record, ECF No. 22, and, at the request of Court, see Min. Order (June 25, 2019), submitted the entire administrative record, totaling 1809 Pages and with documents dating from 1989 to 2018, see ECF No. 38 (AR 1–141, 270–401, 437–74); ECF No. 39 (AR 475–754); ECF No. 40 (AR 755–1057); ECF No. 41 (AR 1058–1426); ECF No. 42 (AR 1427–1809); ECF No. 43 (sealed) (AR 142–269, 402–36). Consistent with Local Civil Rule 7(n), the portions of the administrative record cited or otherwise relied upon in the parties' briefing have been separately docketed, see Joint Appendix, ECF No 48. For clarity, "AR" citations are to the full administrative record, rather than to the joint appendix. Pursuant to a protective order entered in this case, see Protective Order, ECF No. 21, two documents in the administrative record and joint appendix have been filed under seal. These two documents are unsealed to the extent that they are relied upon in this Memorandum Opinion. See In re WP Co. LLC, 201 F. Supp. 3d 109, 116 n.4 (D.D.C. 2016) (citing United States v. Reeves, 586 F.3d 20, 22 n.1 (D.C. Cir. 2009)).

### 2. New Drug Exclusivity

Permitting new-drug sponsors to rely upon a competitor's safety and efficacy investigations risks free riding. See Otsuka II, 869 F.3d at 990. To forestall that problem, the Hatch-Waxman Amendments also established conditions under which new drugs are entitled to a period of market exclusivity. See Hatch-Waxman Amendments § 103(b). Blending streamlined paths for a new-drug sponsor to obtain FDA approval with exclusivity protections was designed "to balance the need to 'make available more low cost generic drugs by establishing a generic approval procedure' with new incentives for drug development in the form of exclusivity and patent term extensions." AR 411 (sealed) (quoting H.R. Rep. No. 98-857, pt. 1, at 14–15 (1984), as reprinted in 1984 U.S.C.C.A.N. 2647–48). Additionally, "[t]hese pathways permit sponsors to rely on what is already known about the previously approved drug, which both allows for speedier market entry than would be possible with a full, standalone 505(b)(1) [new drug application] and leads to increased competition." AR 411 (sealed); see also Otsuka Pharm. Co. v. Burwell ("Otsuka I"), 302 F. Supp. 3d 375, 382 (D.D.C. 2016) (explaining that the Hatch-Waxman Amendments balanced "two competing interests in the pharmaceutical industry: (1) inducing pioneering research and development of new drugs[,] and (2) enabling competitors to bring low-cost, generic copies of those drugs to market").

One form of exclusivity lies at the crux of the parties' dispute. In full, the relevant provision reads:

> If an application submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b), is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the

> application under subsection (b) if the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if 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(c)(3)(E)(iii) (italics and underlining added). The italicized portion of the statute is referred to as the "eligibility clause" and the underlined portion as the "bar clause." See AR 414 (sealed); see also Otsuka I, 302 F. Supp. 3d at 392 (adopting this naming convention). By regulations not challenged here, the FDA has expanded on the meaning of certain terms in the eligibility clause, namely: "active ingredient" has been construed to mean "active moiety," 21 C.F.R. § 314.108(b)(4)(iii),[3] and "new clinical investigation" has been defined to mean an investigation producing results "which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population" and which are not duplicative of "the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product," id. § 314.108(a). In sum, then, § 355(c)(3)(E)(iii) "confers exclusivity when a pharmaceutical company obtains approval to market a previously approved active moiety in a new formulation or for new purposes, and doing so requires it to furnish new clinical investigations to the FDA. With regard to the scope of drugs affected by the three-year exclusivity period, the FDA may not approve an abbreviated application for the same 'conditions of approval of such drug in the [first-in-time] application.'" Otsuka II, 869 F.3d at 990.

[3] The active moiety "is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." 21 C.F.R. § 314.3(b).

### 3. Orphan Drug Exclusivity

A second form of exclusivity—orphan-drug exclusivity ("ODE")—lurks in the background of this case. In 2017, Congress amended the circumstances under which a drug is entitled to ODE. See FDA Reauthorization Act of 2017 ("FDARA"), Pub. L. 115-52, 131 Stat. 1005. For this case, what spurred those amendments matters as much as the current statute governing ODE and, thus, this section addresses both.

Before a new-drug sponsor applies for approval under § 355(b), the sponsor may ask the FDA "to designate the drug as a drug for a rare disease or condition." 21 U.S.C. § 360bb(a)(1). If the FDA finds that the drug under development will treat a rare disease or condition, the FDA shall designate the drug accordingly. Id. Rare diseases and conditions are those affecting "less than 200,000 persons in the United States" or those for which the treatment drug is not likely to be profitable. Id. § 360bb(a)(2). Drugs that treat diseases or conditions of this sort are known as orphan drugs. Consequently, the designation available under § 360bb is known as orphan-drug designation. By regulation, the FDA requires a drug sponsor seeking orphan-drug designation for "a drug that is otherwise the same drug as an already approved drug" to "present a plausible hypothesis that its drug may be clinically superior to the first drug." 21 C.F.R. § 316.20(a).

Orphan-designated drugs receive 7-year exclusivity periods under the conditions set forth in 21 U.S.C. § 360cc. Before Congress passed FDARA in 2017, § 360cc provided, with exceptions not relevant here, that if the FDA:

> [A]pproves an application filed pursuant to section 355 of this title . . . for a drug designated under section 360bb of this title for a rare disease or condition, the [FDA] may not approve another application under section 355 of this title . . . for such drug for such disease or condition for a person who is not the holder of such approved application . . . until the expiration of seven years from the date of the approval of the approved application.

21 U.S.C. § 360cc(a) (2016). The FDA's implementing regulations direct that, "[u]nless FDA previously approved the same drug for the same use or indication, FDA will not approve another sponsor's marketing application for the same drug for the same use or indication before the expiration of 7 years from the date of" the approval of an orphan-designated drug. 21 C.F.R. § 316.31(a). "Same drug," is defined to exclude any subsequent drug "shown to be clinically superior to the first drug." Id. § 316.3(b)(14)(i). The effect of these regulations is that an orphan-designated drug sharing the same use or indication as a previously approved orphan-designated drug will not receive ODE unless shown to be clinically superior to the prior version. Eagle Pharms., Inc. v. Azar, No. 16-cv-790 (TJK), 2018 WL 3838265, at *2 (D.D.C. June 8, 2018). The purpose of these regulations is to undercut "'evergreening' of [ODE]," meaning "the possibility of repeating the seven-year exclusivity period . . . ." Id. (citing Orphan Drug Regulations, 78 Fed. Reg. 35,117, 35,127 (June 12, 2013)).

In 2011, the FDA considered the ODE eligibility of a drug product called Gralise. See *Depomed, Inc. v. U.S. Dep't of Health & Human Servs.*, 66 F. Supp. 3d 217, 226 (D.D.C. 2014).[4] A year earlier, Gralise had received orphan-drug designation after its sponsor presented a plausible hypothesis that Gralise was clinically superior to an orphan drug already approved to treat the rare disease Gralise that treated. Id. at 225–26. The FDA approved the § 355(b)(2) application for Gralise the next year, but denied Gralise ODE because its sponsor had not subsequently proven that Gralise was clinically superior to the already-approved drug. Id. at 226. Gralise's sponsor then challenged, as contrary to the text of § 360cc(a), the FDA rule that

[4] In 2013, the FDA made "minor improvements" to its regulations implementing the Orphan Drug Act, see Orphan Drug Regulations, 78 Fed. Reg. at 35,117, such that the regulations applicable to the FDA's decisionmaking under review in Depomed differ somewhat from the current versions. Those "minor improvements," however, did not make substantive changes, and so Depomed's discussion of when, under the FDA's regulations, a drug is entitled to, or subject to, ODE is no less relevant.

an orphan-designated drug approved for marketing must prove its clinical superiority to the earlier-approved drug before receiving ODE. The Court agreed, ruling that forcing the sponsor of a drug, which already has received orphan designation and is subsequently approved for marketing, to prove its clinical superiority as a condition of ODE contravened the statute. Id. at 229–33. "[T]he plain language of [§ 360cc(a)] means precisely what it says, to wit, when a drug, like Gralise, has obtained both orphan-drug designation and marketing approval, the FDA is precluded from approving any other such drug for seven years from the date of approval." Id. at 233. Therefore, Gralise was entitled to ODE. Id. at 237.

Despite Depomed, the FDA announced that the challenged regulation would continue to be applied. Policy on Orphan-Drug Exclusivity; Clarification, 79 Fed. Reg. 76,888-01 (Dec. 23, 2014). In 2017, Congress passed FDARA, which amended § 360cc to reflect the FDA's regulatory practice. Consequently, under the new version of the statute, if the sponsor of a drug designated under § 360bb seeks ODE, but the drug "is otherwise the same, as determined by the [FDA], as an already approved or licensed drug for " and treats "the same rare disease or condition as the already approved drug," the new drug's sponsor must "demonstrate that such drug is clinically superior to any already approved or licensed drug that is the same drug" as a condition of receiving ODE. 21 U.S.C. § 360cc(c)(1). "Clinically superior" means "that the drug provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, or by providing a major contribution to patient care." Id. § 360cc(c)(2). Additionally, and relevant here, FDARA's "Rule of Construction" instructs that "[n]othing in the amendments . . . shall affect any determination under . . . (21 U.S.C. 360bb, 360cc) made prior to the date of enactment of the [FDARA]." FDARA § 607(b), 131 Stat. at 1050.

### B. FDA Approval of Drugs to Treat Opioid Use Disorder

Opioid use is a public health emergency, with millions of Americans misusing prescription opioids, leading to 33,091 deaths in 2015 alone. AR 162 (sealed). Two million adults have been identified as suffering from OUD, AR 162 (sealed), which "is a chronic, relapsing disease characterized by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and physical consequences," AR 158 (sealed).

One effective method of treating OUD is through prescription opioids themselves. AR 163–64 (sealed). Buprenorphine is one such opioid, which operates as a "partial agonist," AR 163 (sealed), by attaching to, and activating, a nerve cell's opioid receptor and creating the same effect as an illicit opioid, thereby relieving the urge to use opioids, AR 164 (sealed). A partial agonist such as buprenorphine has effects like a full agonist, but the effects "are understood to reach a 'ceiling' at moderate doses, beyond which increasing doses of the drug do not produce the increased effect that would result from full opioid agonists." AR 165 (sealed). A supposed benefit of that ceiling is to "limit its attractiveness as a drug of abuse." AR 165 (sealed).

#### 1. Early Approval of Buprenorphine Drugs

The FDA first approved buprenorphine in 1981 as a pain medication. AR 164 (sealed), 404 (sealed). In 1994, Indivior obtained orphan designation for Subutex, a sublingual buprenorphine product, to treat opioid dependence, Defs.' Reply Supp. Cross-Mot. Summ. J. ("Defs.' Reply") at 23, ECF No. 46; AR 66, and then, in 2002, the FDA approved Indivior's application to market Subutex, AR 164 (sealed), 404 (sealed).[5] Subutex was the first approved use of buprenorphine to treat an opioid-related disease. AR 404 (sealed). Since the first

[5] "Sublingual products are those administered via absorption through the mouth under the tongue and are a type of transmucosal product." Defs.' Mem. Supp. Cross-Mot. Summ. J. & Opp'n Pl.'s Mot. Summ. J. ("Defs.' Mem.") at 10 n.11, ECF No. 28-1. For purposes of this opinion, references to sublingual or transmucosal versions of buprenorphine can be understood to mean versions of the drug taken orally.

approved uses of buprenorphine as a treatment for OUD, other drugs that deliver a sublingual, daily dose of buprenorphine have been approved. AR 164 (sealed).

**2. Approval of Extended-Release Buprenorphine Drugs to Treat OUD**

Although several drugs that deliver a daily dose of buprenorphine have received FDA approval, these products come with certain risks. "[W]hen a partial agonist displaces a full agonist at the receptor, the relative reduction in receptor activation can produce withdrawal effects," such that "[i]ndividuals dependent on full agonists may therefore experience sudden and severe symptoms of withdrawal." AR 165 (sealed). Additionally, the euphorigenic effects of even a partial agonist like buprenorphine are strong enough to create an illicit market. AR 165 (sealed). Furthermore, unintentionally exposing children to buprenorphine may be harmful. AR 156 (sealed), 165 (sealed), 1221. Separate from risks associated with a partial agonist, daily-dosing delivery systems pose difficulties attendant to requiring that a patient self-administer the drug for an extended period at home. AR 1221. Accordingly, the FDA has encouraged pharmaceutical companies to devise methods of administering buprenorphine that mitigate these risks, specifically promoting "well-tolerated, less burdensome treatments, with reduced liability for abuse, misuse, and overdose." AR 156 (sealed).

(a) Probuphine

Probuphine, which the FDA approved in May 2016, is one drug that satisfies some of those criteria. AR 404–06 (sealed). Probuphine is a "6-month subdermal implant for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on [8mg per day or less] of a transmucosal buprenorphine-containing product." AR 404 (sealed).

(b) Sublocade

Sublocade is a second drug to treat OUD that mitigates some of the risks associated with daily, self-administered doses of buprenorphine. Sublocade is an injectable depot that "provides sustained plasma levels of buprenorphine sufficient to block the effects of exogenous opioids over a minimum of 28 days and is intended for the treatment of moderate to severe . . . OUD in patients who have undergone treatment initiation and dose-stabilization with a transmucosal buprenorphine-containing product." AR 12. On May 30, 2017, Indivior filed a new-drug application under § 355(b)(2) for Sublocade, AR 1, which the FDA approved on November 30, 2017, AR 1.

Two new clinical investigations were essential to Sublocade's approval. AR 420 (sealed). The first tested how well Sublocade inhibited the subjective effects of opioid use. AR 31, 407 (sealed). Before participants in that study were treated with Sublocade, they were treated for up to 14 days on 8mg to 24mg per day of Suboxone, a drug that administers buprenorphine sublingually, to achieve dose stabilization, AR 31, which is the brief process of identifying the dose of buprenorphine needed to mitigate precipitated withdrawal symptoms, AR 65, 407 n.21 (sealed). Participants able to complete the stabilization phase received a 300mg injection of Sublocade on the first and twenty-ninth days of the study. AR 31–33. At different days across the study, participants were injected with either a narcotic or a placebo and asked to measure their "drug liking." AR 33. This study showed that "drug liking" scores for participants receiving Sublocade were not higher than participants receiving a placebo. AR 33 (sealed). The second investigation tested the efficacy, safety, and tolerability of multiple Sublocade injections over a 24-week period. AR 43. Again, participants started on Suboxone for three days, and then dose adjusted for between four and 11 days. AR 43, 407 (sealed). Participants who managed the

stabilization phase (and who were not randomly selected for a placebo) were randomized between a path on which they received a 300mg dose of Sublocade once per month for six months or a path on which they received two monthly doses of 300mg Sublocade, followed by four monthly doses of 100mg Sublocade. AR 43, 407 (sealed). This study showed that Sublocade blocked the effects of opioid use for the entire period between doses. AR 45, 408 (sealed).

(c) Brixadi

Brixadi is a third drug that treats OUD while addressing the risks associated with daily, self-administered doses of buprenorphine. Braeburn submitted a § 355(b)(2) application in the summer of 2017 for Brixadi, shortly after Indivior had filed its application for Sublocade. AR 142 (sealed), 152 (sealed). Like Sublocade, Brixadi is an "extended-release formulation of buprenorphine . . . for the treatment of moderate to severe . . . OUD in adults." AR 152 (sealed). Unlike Sublocade, Brixadi comes in both a weekly and monthly depot version. AR 152 (sealed).[6]

Braeburn's application for approval of Brixadi relied on three of its own clinical investigations of the drug's safety and effectiveness in both versions. AR 409 (sealed). The first study involved stabilizing participants with an oral opioid for three to seven days, AR 185 (sealed), and then administering Brixadi Weekly for seven weeks, AR 183 (sealed), and showed that 24mg and 32mg doses of Brixadi Weekly inhibit the subjective effects of opioid use, AR 183 (sealed), 409 (sealed). The second study involved participants who were new to buprenorphine treatment, each of whom received a 4mg test dose of buprenorphine, AR 194–196

[6] Brixadi Weekly and Monthly are formulated slightly differently, AR 275, containing different proportions of "buprenorphine base," and different percentages of "w/w anhydrous ethanol soybean phosphatidylcholine/ glycerol dioleate" in different weight ratios, AR 307–08. These distinctions are irrelevant for this case.

(sealed), 200 (sealed), 409 (sealed), followed by an injection of Brixadi Weekly, AR 194 (sealed), 199 (sealed), 202 (sealed). After taking the weekly product for 12 weeks, participants transitioned to Brixadi Monthly. AR 194 (sealed), 202 (sealed). This investigation demonstrated that Brixadi "would be appropriate for use from the first patient visit . . . so that no take-home house of sublingual buprenorphine would be necessary in the real-world setting." AR 194 (sealed). A third study confirmed the safety of Brixadi Weekly and Monthly over an extended period, AR 178 (sealed), 180 (sealed), 225 (sealed), and involved participants, who were both new-to-treatment and transitioning from prior buprenorphine treatment, AR 178–180 (sealed), 225 (sealed), with new-to-treatment patients all starting on Brixadi Weekly, AR 234 (sealed).

On December 21, 2018, the FDA tentatively approved Braeburn's application for Brixadi. AR 270. Prescribing information included with the tentative approval specified that before taking Brixadi, patients new to buprenorphine should take a 4mg transmucosal test dose to confirm their buprenorphine tolerance without experiencing precipitated withdrawal. AR 278. If the test dose is tolerated, patients may then receive a 16mg dose of Brixadi Weekly, followed three days later by an 8mg dose of the weekly product. AR 278. In the first week of treatment, the patient can receive one more 8mg dose if needed. AR 278–79. After the first week, the patient receives Brixadi Weekly at a volume that matches the total amount of the drug administered in week one. AR 278–79. While new-to-treatment patients may not use Brixadi Monthly, patients already being treated with either a transmucosal buprenorphine product or Brixadi Weekly may transition to one of Brixadi Monthly's doses: 64mg, 96mg, or 128 mg. AR 278–79. Approval for Brixadi Weekly, however, was only tentative pending the FDA's receipt of appropriate labeling from Braeburn, a step Braeburn has not taken, AR 403 (sealed), and approval for Brixadi Monthly was only tentative because that product "is subject to expiration of

a period of patent protection and/or exclusivity" and so final approval "may not be granted before the period has expired," AR 270.

### 3. *FDA's Letter Decision Blocking Final Approval of* Monthly Brixadi

The same day that the FDA sent Braeburn the tentative approval letter, the FDA's Center for Drug Evaluation and Research Exclusivity Board issued a letter decision ("Letter Decision") explaining why Brixadi Monthly was not eligible for final approval. See generally AR 402–36 (sealed). The agency assessed whether Brixadi Monthly was blocked by the three-year exclusivity, under § 355(c)(3)(E)(iii), belonging to Probuphine or Sublocade. AR 403 (sealed). While Probuphine's exclusivity, the FDA decided, did not bar market entry for either Brixadi product, Sublocade's exclusivity, which does not expire until November 30, 2020, prevented final approval of Brixadi Monthly. AR 403 (sealed).

The Letter Decision explained that the FDA interprets the phrase "for the conditions of approval," the operative language in § 355(c)(3)(E)(iii)'s bar clause, to mean that the FDA may not approve any application under § 355(b) for a drug product that shares the exclusivity-eligible drug's "innovation represented by its approved drug product that is supported by new clinical investigations essential to approval." AR 416 (sealed). Thus, § 355(c)(3)(E)(iii) prevents the FDA from approving a drug application if the applied-for drug shares a quality that the FDA deems another drug sponsor to have innovated and to have obtained approval for in the prior three years. AR 416 (sealed). At the same time, "[e]xclusivity does not extend beyond the scope of the approval and does not cover aspects of the drug product for which new clinical investigations were not essential." AR 415–16 (sealed).

For Probuphine, the protected innovation was a "subdermal implant product for a 6-month period, for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal

buprenorphine containing product." AR 420 (sealed). Brixadi's did not share that innovation because it was not "a 6-month subdermal implant, but rather, [a] weekly and monthly depot injection[] of buprenorphine." AR 420 (sealed). Moreover, Brixadi is "for use in a different patient population than that for which Probuphine is approved, not limited to patients who have been stable on a low to moderate dose of buprenorphine for multiple months." AR 420 (sealed).

For Sublocade, the clinical studies essential to Sublocade's approval demonstrated only that a monthly depot would be effective and only to treat moderate to severe OUD. AR 421 (sealed). Consequently, Sublocade's innovation, and exclusivity, extended only to "the dosing interval provided by the monthly depot product that delivered an appropriate amount of buprenorphine over a one-month period to treat moderate to severe OUD." AR 421 (sealed). The agency found that Sublocade's exclusivity was not, however, "constrained by the use of the specific treatment initiation or dose adjustment schedule, or to the strengths for which it is approved" because the drug's ability to deliver the right amount of buprenorphine through a monthly depot "is not necessarily limited to or dependent on the particular treatment initiation, dose adjustment schedule, or strengths." AR 421–22 (sealed). In the agency's view, if Sublocade's innovation were limited by those features, the drug's exclusivity would be narrower than its innovation. AR 422 (sealed). Sublocade blocked Brixadi Monthly because both are "a monthly depot buprenorphine product to treat moderate to severe OUD." AR 422 (sealed). Sublocade did not block the weekly product because of the different dosing interval. AR 422 (sealed).

While Braeburn had argued that "certain features of the way the Sublocade studies were conducted impacts whether Sublocade's exclusivity blocks approval of Brixadi," the agency disagreed. AR 427 (sealed). Those features of the clinical studies were found to be "not

meaningfully different when comparing Sublocade with the monthly version of Brixadi," AR 427 (sealed), or irrelevant because Brixadi Monthly still "shares the exclusivity-protected conditions of approval," AR 429 (sealed); see also AR 429 n.89 (sealed) (rejecting clinical significance of differences between Sublocade and Brixadi Monthly). In other words, while acknowledging "differences between Sublocade and Braeburn's proposed monthly depot products," the agency rejected Braeburn's position that those differences were significant for exclusivity since "the relevant aspect of the subsequent application for purposes of this analysis is that it also seeks to deliver buprenorphine via a depot dosage form over a monthly period to treat moderate to severe OUD." AR 430. Finally, the agency rejected Braeburn's contention that Brixadi Weekly and Monthly are an integrated system, determining that "[u]se of the monthly product is not dependent on use of the weekly product, or vice versa." AR 435 (sealed).

Independent of the FDA's determination that Sublocade's three-year exclusivity bars final approval of Brixadi Monthly, on April 5, 2019, Braeburn petitioned the FDA to "revoke orphan drug designation . . . for Sublocade . . . injection for treatment of opiate addiction in opiate users." Citizen Petition from Goodwin Proctor, LLP on behalf of Braeburn, Inc. ("Citizen Petition") at 1, No. FDA-2019-P-1679-0001 (Apr. 5, 2019), available at https://www.regulations.gov/document?D=FDA-2019-P-1679-0001. Sublocade, the petition contended, should not be orphan-designated because OUD affects more than two million Americans and Sublocade will easily recoup its development costs and thus failed to meet the prerequisites of a rare or unprofitable drug to qualify for orphan-drug designation. Id. at 1–2.

### C. Procedural Background

About four months following issuance of the Letter Decision, Braeburn instituted this action on April 9, 2019, filing a two-count complaint alleging that the FDA's determination of Sublocade's exclusivity violated 5 U.S.C. § 706(2)(A) of the Administrative Procedure Act

("APA") and 21 U.S.C. § 355(c)(3)(E)(iii). Compl. ¶¶ 72–83. The same day, Braeburn filed a motion for a preliminary injunction to enjoin the FDA from relying on Sublocade's exclusivity to bar final approval of Brixadi Monthly. See Mot. Prelim. Inj., ECF No. 7

Two days later, Indivior filed an unopposed motion to intervene. See Mot. Intervene. That motion was granted the next day, 1st Min. Order (Apr. 12, 2019), and the parties proposed entry of an order expediting briefing on the merits rather than resolving the motion for preliminary injunction, Joint Status Report (Apr. 12, 2019). Consistent with the parties' request, the Court entered a scheduling order for expedited briefing on cross-motions for summary judgment. 2nd Min. Order (Apr. 12, 2019).

Briefing proceeded under the parties' schedule, with the final briefs filed on July 1, 2019. See Defs.' Reply; Intervenor-Def.'s Reply Supp. Cross-Mot. Summ. J. ("Intervenor-Def.'s Reply"), ECF No. 44. The Court held a hearing on July 15, 2019. The parties' cross-motions for summary judgment are now ripe for resolution.

## II. LEGAL STANDARD

Under the APA, a reviewing Court sets aside agency action that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). In APA cases involving cross-motions for summary judgment, "the district judge sits as an appellate tribunal. The 'entire case' on review is a question of law." Am. Bioscience, Inc. v. Thompson, 269 F.3d 1077, 1083 (D.C. Cir. 2001). Accordingly, this Court need not and ought not engage in lengthy fact finding, since "[g]enerally speaking, district courts reviewing agency action under the APA's arbitrary and capricious standard do not resolve factual issues, but operate instead as appellate courts resolving legal questions." James Madison Ltd. by Hecht v. Ludwig, 82 F.3d 1085, 1096 (D.C. Cir. 1996); see also *Lacson v. U.S. Dep't of Homeland Sec.*, 726 F.3d 170, 171

(D.C. Cir. 2013) (noting, in APA case, that "determining the facts is generally the agency's responsibility, not ours").

## III. DISCUSSION

Braeburn challenges the Letter Decision as being both contrary to § 355(c)(3)(E)(iii) and as being arbitrary and capricious due to its internal inconsistencies and departures from agency precedent. The FDA and Indivior disagree with each contention. Separately, Indivior argues that Braeburn does not have standing to challenge the Letter Decision. Braeburn's standing to bring this action is considered first before turning to Braeburn's arguments.

### A. Standing

The Constitution extends "the judicial power" only to "Cases" and "Controversies." U.S. CONST. art. III, § 2. That limit is policed through the standing doctrine, which, in turn, depends on whether the plaintiff suffered an injury that can be traced to the defendant's challenged conduct, and that a court can redress with a decision in the plaintiff's favor. Spokeo, Inc. v. Robins, 136 S. Ct. 1540, 1547 (2016). "[E]ach element of Article III standing 'must be supported in the same way as any other matter on which the plaintiff bears the burden of proof, i.e., with the manner and degree of evidence required at the successive stages of litigation.'" Bennett v. Spear, 520 U.S. 154, 167–68 (1997) (quoting Lujan v. Defenders of Wildlife, 504 U.S. 555, 561 (1992)). At the summary judgment stage, the plaintiff may establish standing by affidavit. Id. at 168.

As Braeburn notes, "the D.C. Circuit has made clear that 'in many if not most cases the petitioner's standing to seek review of administrative action is self-evident' from the administrative record." Pl.'s Opp'n Defs.' & Intervenor-Def.'s Cross-Mots. Summ. J. & Reply Supp. Pl.'s Mot. Summ. J. ("Pl.'s Opp'n") at 33, ECF No. 33 (quoting Fund for Animals, Inc. v. Norton, 322 F.3d 728, 733 (D.C. Cir. 2003)). Beyond that, Braeburn has provided an affidavit

attesting to the economic injuries that it has sustained, and is sustaining, due to the FDA's determination that Sublocade's three-year exclusivity bars final approval of Brixadi Monthly. See Pl.'s Opp'n, Decl. of Michael Derkacz ¶¶ 8–16, 20, ECF No. 33-1. Of course, as Braeburn also highlights, "[e]conomic harm to a business clearly constitutes injury-in-fact." Pl.'s Opp'n at 33 (quoting Carpenters Indus. Council v. Zinke, 854 F.3d 1, 5 (D.C. Cir. 2017)).

Nevertheless, Indivior insists that Braeburn lacks standing because the FDA's determination that Brixadi Monthly cannot be marketed until Sublocade's right to exclusivity expires in November 2020 is not causing any harm separate from the harm Braeburn will suffer due to Sublocade's right to ODE through 2024. Intervenor-Def.'s Mem. Supp. Cross-Mot. Summ. J. & Opp'n Pl.'s Mot. Summ. J. ("Intervenor-Def.'s Mem.") at 21–22, ECF No. 26-1. Sublocade's right to ODE, Indivior presses, severs the causal connection between Braeburn's purported injuries and the FDA's challenged exclusivity determination, and leaves the Court without the means to redress Braeburn's injuries. Id. at 22; Intervenor-Def.'s Reply at 2.

Indivior's standing argument is unconvincing. To begin, as Indivior readily concedes, the FDA has not resolved whether Sublocade is entitled to ODE. See Intervenor-Def.'s Reply at 3; see also Defs.' Reply at 23 ("FDA has not yet determined whether Sublocade is entitled to a seven-year period of [ODE] that would block the approval of Brixadi Weekly or Monthly."). Properly framed, then, Indivior's argument is that a hypothesized future event that might injure Braeburn in the same way as the challenged agency decision leaves Braeburn without standing. In that light, the frailty of Indivior's standing argument emerges. Braeburn's access to judicial relief does not require that it disprove any speculated alternative source of injury that Indivior conjures, but only that it marshals evidence of injury, causation, and redressability sufficient for the summary judgment stage. See Duke Power Co. v. Carolina Envtl. Study Grp., Inc., 438 U.S.

59, 78 (1978) ("Nothing in our prior cases requires a party seeking to invoke federal jurisdiction to negate the kind of speculative and hypothetical possibilities suggested in order to demonstrate the likely effectiveness of judicial relief."); see also *Int'l Ladies' Garment Workers' Union v.* Donovan, 722 F.2d 795, 811 (D.C. Cir. 1983) ("The appellants need not negate every conceivable impediment to effective relief no matter how speculative . . . nor are they required to prove that granting the requested relief is certain to alleviate their injury." (emphasis in original) (internal quotations omitted)).

Indivior rejects that characterization of its argument, maintaining that Sublocade's right to ODE is not speculative, but certain.[7] To arrive at that conclusion, Indivior invokes the interpretation of § 360cc articulated in Depomed, in which the pre-FDARA version of § 360cc was read to confer a right to ODE that follows automatically from the approval of any § 355(b) application for a drug already orphan-designated under § 360bb. 66 F. Supp. 3d at 229–33. Indivior reasons that having received orphan designation for buprenorphine, AR 66, and having its § 355(b) application for Sublocade approved, AR 1, Sublocade has a "current legal entitlement to ODE," Intervenor-Def.'s Mem. at 22, that "sprang automatically from Indivior's pre-FDARA possession of an orphan designation for buprenorphine to treat OUD, and so was fully intact when FDARA took effect," Intervenor-Def.'s Reply at 5.

Despite the proclaimed entitlement, whether Sublocade will earn ODE remains, at this juncture, speculative. Contrary to Indivior's assertion, Sublocade did not have a fully intact right to ODE when FDARA took effect. Depomed identified two conditions that, when both were

[7] Both Braeburn and Indivior agree that no judicial ruling now about Sublocade's right to ODE would be appropriate. Pl.'s Opp'n at 33, 39; Intervenor-Def.'s Mem. at 25–27. Indivior suggests, in the alternative, that these proceedings might be stayed pending the FDA's resolution of whether Sublocade is entitled to ODE, which resolution may affect Braeburn's ability to market Brixadi. Intervenor-Def.'s Mem. at 27, 44. Indivior advances no real argument as to why such a stay would be appropriate, and the Court cannot discern one.

satisfied, bestowed ODE: (1) orphan designation and (2) approval of the orphan-designated drug's § 355(b) application. 66 F. Supp. 3d at 229–33. When FDARA added a third criterion—that the drug's sponsor shows clinical superiority to any already-approved version of same drug, see 21 U.S.C. § 360cc(c)(1)—Sublocade had not yet been approved and thus had not satisfied both conditions of the pre-FDARA version of § 360cc.

Alternatively, Indivior insists that even if Sublocade had no existing right to ODE at the time FDARA was passed, Sublocade's current right to ODE is certain because Sublocade is subject to the pre-FDARA version of § 360cc, and thus not beholden to the newly enacted clinical superiority requirement under § 360cc(c). Intervenor-Def.'s Reply at 5–8. That argument relies on the FDARA's Rule of Construction, which directs that the statute's amendments shall not "affect any determination under . . . (21 U.S.C. 360bb, 360cc) made prior to the date of enactment of the [FDARA]." FDARA § 607(b), 131 Stat. at 1050. Indivior understands the Rule of Construction to require that Sublocade's right to ODE be assessed under the pre-FDARA version of § 360cc because, before FDARA, ODE followed from a single determination: the FDA's determination to orphan-designate a drug under § 360bb. Intervenor-Def.'s Reply at 5–6. Not rewarding Sublocade with ODE would affect that determination. Further, Indivior reasons, FDARA amended only § 360cc, but the Rule of Construction directs that the amendments shall not affect any determination under § 360cc or § 360bb. Id. at 6–7. According to Indivior, including a reference to § 360bb in the Rule of Construction respects the benefits attendant to a designation under that section. Id.

Despite Indivior's reasoning, how to apply FDARA to a drug that had been orphan-designated before FDARA, but not approved under § 355(b) until after FDARA was enacted, is uncertain. Plausibly read, leaving intact Indivior's receipt of orphan designation while applying

§ 360cc(c)'s new standard respects the only actual determination made prior to FDARA (i.e., the orphan-drug designation), even if application of this new standard affects a possible consequence of that determination. Either way, Sublocade is still orphan-designated. In the end, no resolution of how § 360cc applies here is reached, but FDARA's amendments are one reason that Sublocade's entitlement to ODE is not inevitable.

If Sublocade's entitlement to ODE falls under the current version of § 360cc, the drug's right to ODE depends on the FDA finding that Sublocade is clinically superior to prior versions of the same drug that received ODE. Indivior points to nothing in the record showing that the FDA has made such a determination. Moreover, even if Sublocade were found to be clinically superior to past versions of the same drug, the FDA might determine that Brixadi Monthly is clinically superior to Sublocade and thus not subject to Sublocade's ODE. 21 C.F.R. §§ 316.3(b)(14), 316.31(a). Again, resolution of these issues is not necessary here, but merely recognizing them as possibilities adds layers of doubt to Indivior's prognostications.

Finally, as of April 5, 2019, the FDA has under consideration a citizen petition filed by Braeburn to strip Indivior of the orphan designation received for buprenorphine, which dates back over 25 years. See generally Citizen Petition. In brief, the petition contends that buprenorphine should not be orphan-designated now because OUD is not a rare disease and the FDA's analysis of whether a buprenorphine drug used to treat OUD would be profitable was inaccurate. Id. at 1–2. If that petition succeeds, Sublocade will lose its predicate for ODE. Together, these considerations show that the prospect of Sublocade receiving ODE, and thus the possibility of an independent source of Braeburn's purported injury, is uncertain.

Despite the current uncertainty of Sublocade's right to ODE, Indivior relies primarily on two cases as support for the proposition that Braeburn does not have constitutional standing.

Each case misses the mark. First, Indivior cites Clapper v. Amnesty International USA, 568 U.S. 398 (2013), see Intervenor-Def.'s Mem. at 23, in which the Supreme Court held that the plaintiffs did not have standing to challenge a federal surveillance statute because they could "only speculate" as to whether any of them would be subject to surveillance under the challenged statute and because the government had "numerous other methods of conducting surveillance, none of which is challenged here." Clapper, 568 U.S. at 412–13. Clapper is distinguishable from the instant case twice over: (1) Braeburn is challenging a statute that already has been applied to its detriment; and (2) whether ODE is a second reason that the government may deny final approval of Brixadi Monthly is uncertain and, in any event, being challenged through Braeburn's citizen petition.

In Teva Pharmaceuticals USA v. Azar, 369 F. Supp. 3d 183 (D.D.C. 2019), a second case Indivior cites, see Intervenor-Def.'s Mem. at 23–24, Teva did not have standing to challenge the FDA's interpretation of "first applicant," as used in 21 U.S.C. § 355(j)(5)(B)(iv), which interpretation the FDA had adopted in a letter decision unrelated to Teva, Teva, 369 F. Supp. 3d at 192. Even if the FDA might have soon applied the same interpretation to determine that Teva was not a "first applicant" entitled to the concomitant benefits, Teva lacked standing because, "most significantly," whether Teva would have received those benefits was speculative given that a related statutory provision created situations in which a qualifying "first applicant" may forfeit the very same benefits. Id. at 203–04. Here, for the reasons just examined, the speculative proposition is that Sublocade's right to ODE will cause the same injury to Braeburn that the FDA's exclusivity decision has.

Moreover, if a forfeiture were to deprive Teva of the benefits attendant to "first applicant" status, Teva would not be able to point to any agency decision causing an injury. Id.

at 204–05. By contrast, no matter the FDA's eventual ODE decision, no speculation is needed to see that the FDA's determination of Sublocade's exclusivity independently is a reason that Braeburn may not market Brixadi Monthly right now. The sole existing cause of Braeburn's injury would be remedied with a decision in Braeburn's favor.

Finally, Indivior contends that standing does not exist if policy decisions are an independent cause of the same injury. Intervenor-Def.'s Mem. at 24 (citing Allen v. Wright, 468 U.S. 737 (1984) and Black v. LaHood, 882 F. Supp. 2d 98 (D.D.C. 2012)). In Allen, the plaintiff challenged the IRS's failure to revoke tax exemptions from racially-segregated private schools. 468 U.S. at 740–45. One of the plaintiffs' alleged injuries—"their children's diminished ability to receive an education in a racially integrated school"—undoubtedly was cognizable, but that injury was not traceable to the tax exemptions because, among other reasons, "it [was] entirely speculative . . . whether withdrawal of a tax exemption from any particular school would lead the school to change policies." Id. at 756–58. Nothing comparable is at play here as no third-party policy would keep Brixadi Monthly from the market even if the Letter Decision were vacated. For the exact same reason, Black is inapposite. 882 F. Supp. 2d at 106–07 (finding that the plaintiffs did not have standing to challenge an agency's environmental analysis of converting a road to a pedestrian trail because the alleged injury—depriving vehicles of access to the road—would be redressed only if the local council revisited a prior decision to close the road to vehicles).

As things stand, only one decision stops Braeburn from marketing Brixadi Monthly: the FDA's determination of Sublocade's right to three-year exclusivity. A decision in Braeburn's favor here would remedy that harm. Even if Indivior were able to make a strong case for ODE, vacating the FDA's challenged exclusivity determination would clear at least one of two

independent reasons Braeburn may not market Brixadi Monthly. Such a decision would increase the likelihood of redressing Braeburn's injury. For standing, that is enough. See Czyzewski v. Jevic Holding Corp., 137 S. Ct. 973, 983 (2017) ("Consequently, the Bankruptcy Court's approval of the structured dismissal cost petitioners something. They lost a chance to obtain a settlement that respected their priority."); cf. Monsanto Co. v. Geertson Seed Farms, 561 U.S. 139, 152–53 (2010) ("[T]here is more than a strong likelihood that [the agency] would partially deregulate [a plant product] were it not for the District Court's injunction. The District Court's elimination of that likelihood is plainly sufficient to establish a constitutionally cognizable injury."). Therefore, Braeburn has standing to challenge the Letter Decision.

### B. The FDA's Interpretation of the FDCA

Turning to the merits, Braeburn's first contention is that the FDA's exclusivity determination is premised on an interpretation of the FDCA that is contrary to the statute. If true, the exclusivity determination would be "not in accordance with law." 5 U.S.C. § 706(2)(A).

An agency's interpretation of a statute it administers generally is reviewed under the two-step inquiry set out in Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837 (1984). See Cal. Cmtys. Against Toxics v. EPA, – F.3d – , No. 18-1163, 2019 WL 2750852, at *6 (D.C. Cir. July 2, 2019). Chevron's framework applies to an FDA interpretation of the FDCA set forth in a letter decision. AstraZeneca Pharms. LP v. FDA, 713 F.3d 1134, 1139 (D.C. Cir. 2013).

At Step One, the court asks whether "Congress has directly spoken to the precise question at issue." Chevron, 467 U.S. at 842. If so, the Court "must give effect to the unambiguously expressed intent of Congress." Id. at 843; see also Kisor v. Wilkie, 139 S. Ct. 2400, 2415 (2019) ("[I]f the law gives an answer—if there is only one reasonable construction of

a regulation—then a court has no business deferring to any other reading . . . .").[8] If, however, the contested statute can be read in more than one way, or is silent as to the relevant question, the case moves to Step Two. See Van Hollen, Jr. v. FEC, 811 F.3d 486, 495 (D.C. Cir. 2016).

At Step Two, "the question for the court is whether the agency's answer is based on a permissible construction of the statute." Chevron, 467 U.S. at 843. Said differently, the agency's statutory interpretation "must come within the zone of ambiguity the court has identified after employing all its interpretative tools." Kisor, 139 S. Ct. at 2416. In conducting this analysis, Courts "defer to the agency's permissible interpretation, but only if the agency has offered a reasoned explanation for why it chose that interpretation." Vill. of Barrington v. Surface Transp. Bd., 636 F.3d 650, 660 (D.C. Cir. 2011). "This is a requirement an agency can fail." Kisor, 139 S. Ct. at 2416.

**1. Chevron Step One**

The FDA denied final approval for Brixadi Monthly due to Sublocade's right to exclusivity under 21 U.S.C. § 355(c)(3)(E)(iii). Under that provision's bar clause, the FDA "may not make the approval of an application submitted under subsection (b) for the conditions of approval of [an exclusivity-eligible drug product] effective before the expiration of three years from the date of the approval of the [exclusivity-eligible drug product]." 21 U.S.C. § 355(c)(3)(E)(iii). Thus, whether an already-approved drug product bars final approval of a later product depends, in the only way pertinent to this case, on the overlap between "the conditions of approval" of the two products. The precise question here is whether the FDA can

[8] Although Kisor v. Wilkie related to judicial review of an agency's interpretation of its own regulation, the Supreme Court compared the governing standards to those that structure judicial review of an agency's interpretation of a statute it administers. See 139 S. Ct. at 2415–16.

bar final approval of Brixadi Monthly because such approval would be "for the conditions of approval" of Sublocade. That, in turn, depends on the meaning of "the conditions of approval."[9]

Braeburn prevails at Step One only if the meaning of "the conditions of approval" is "susceptible of 'only [one] possible interpretation.'" *Petit v. U.S. Dep't of Educ.*, 675 F.3d 769, 781 (D.C. Cir. 2012) (quoting Cnty. of L.A. v. Shalala, 192 F.3d 1005, 1015 (D.C. Cir. 1999)). This step presents a high hurdle from the outset as "neither the FDCA's overarching definition section nor the particular section at issue here specifically defines the phrase[] 'conditions of approval.'" Otsuka I, 302 F. Supp. 3d at 394; see also Veloxis Pharms., Inc. v. FDA, 109 F. Supp. 3d 104, 120 (D.D.C. 2015) ("Because the parties agree that the term 'conditions of approval' is undefined in the FDCA and that no FDA implementing regulation clarifies the meaning of that term . . . the parties essentially concede that the term is ambiguous."). Of course, not all statutory phrases must be accompanied by a statutory definition for their meaning to be evident. Petit, 675 F.3d at 781. In this instance, a definition would have been useful as "the operative words . . . have multiple potential meanings." Otsuka I, 302 F. Supp. 3d at 394. Contextualizing the relevant phrase provides only some help. Id.

Both the FDA's and Braeburn's interpretation of "the conditions of approval" start from roughly the same spot. Each understands the phrase to refer to some subset of the circumstances for which a drug product has been shown to be safe and effective, and thus approved. See AR 415–16 (sealed); Pl.'s Mem. Supp. Mot. Summ. J. ("Pl.'s Mem.") at 25–26, ECF No. 24-1; Pl.'s

[9] Braeburn's briefs allocate much of the space nested under headings referencing Chevron Step One to arguments that the FDA's interpretation of "the conditions of approval" is unreasonable rather than arguments that the statute supplies an unambiguous meaning for "the conditions of approval." See Pl.'s Mem. at 27–31; Pl.'s Opp'n at 11–14, 16–18. Presumably, Braeburn's strategy reflects a fear that failure at Step One loses the case. See Kent Barnett & Christopher J. Walker, Chevron in the Circuit Courts, 116 MICH. L. REV. 1, 33 (2017) (finding, based on a study of cases in federal courts of appeals decided between 2003 and 2013, that agencies prevailed at Chevron Step Two 93.8% of the time). Nevertheless, most of Braeburn's arguments are better directed at Chevron Step Two.

Opp'n at 13–14.[10] Still, that "the conditions of approval" refers in some manner to the circumstances for which a drug product has, or has not, been approved for use does not answer which of those circumstances are "the conditions of approval." At least four different methods are available to describe the scope of those circumstances.

First, at one extreme, all restrictions on a drug product's legally prescribed use, as described on the product's label, might be "the conditions of approval." No drug product can be approved unless shown to be safe and effective under the specific "conditions prescribed, recommended, or suggested in the proposed labeling," and so, it might reasonably follow, labeling corresponds with the drug product's "conditions of approval." Pl.'s Mem. at 25–26 (quoting 21 U.S.C. § 355(d)). Initially, at least, Braeburn tacks in this direction, suggesting that "the conditions of approval" unambiguously refers to all "the conditions under which the drug is approved for patient use, as stated on the drug's label." Id. at 25. Still, that interpretation does not fit neatly enough to be unambiguously correct. Protecting exclusivity rights only if a follow-on product matches every condition listed in the first product's label would curtail exclusivity narrowly to exclude only precisely identical drug products, a result plainly at odds with Congress's goal of incentivizing research with market exclusivity. For example, Sublocade's

[10] Indivior, on the other hand, reasons that because the "bar clause delays approval of follow-on products 'for the conditions of approval,'" of the first drug, "conditions of approval" means the medical conditions, such as OUD, which the drug is intended to treat. Intervenor-Def.'s Mem. at 32 (emphasis in original). After all, drugs are not approved "for" their limitations. Id. Indivior's interpretation is not particularly persuasive. For one, when "condition" means a medical condition in the FDCA, or related statutes, typically the phrase used is "disease or condition." See, e.g., 21 U.S.C. §§ 355(n)(3)(D), 360bb(a)(1), (2), 360cc(a)(2), (c); but see id. § 355(i)(3)(B)(i) (using "condition" on its own plausibly to refer to a medical condition). Additionally, the plural use of "conditions" in § 355(c)(3)(E)(iii) suggests that the statute is contemplating some combination of the drugs' characteristics. Finally, Indivior's interpretation would expand the right to exclusivity by barring any follow-on drug using the same active ingredient to treat the same condition, no matter the first drug's limits and thereby potentially deprive too many people of necessary drugs, impairing the balance the Hatch-Waxman Amendments were intended to strike. Confusingly, Indivior's response to this overbreadth concern is that the FDA does not actually apply Indivior's interpretation. Intervenor-Def.'s Reply at 18. In any event, the phrase "the conditions of approval" is ambiguous in other respects and the FDA does not employ Indivior's hypothesized interpretation. Thus, to say the least, Indivior's interpretation is unhelpful to the ultimate question of whether the FDA has reasonably interpreted § 355(c)(3)(E)(iii).

labeling says not to store the product at room temperature and to wait 15 minutes for the drug to reach room temperature before injection. AR 99. If "the conditions of approval" encompasses all that appears in a drug product's label, then Braeburn would be out from under Sublocade's exclusivity for creating a product that was identical in all respects save for safe storage at room temperature. Beyond that troubling outcome, reading "the conditions of approval" to mean all restrictions and directions that appear on a label would equate this phrase with, and leave no space for, the phrase "conditions of use prescribed, recommended, or suggested in the proposed labeling," which appears multiple times in the same statute, see 21 U.S.C. § 355(d), (e), (j)(2)(A)(i), and matches better as a reference to the full universe of directions and restrictions contained on a label.

Second, as Braeburn later suggests, "the conditions of approval" might encompass "the conditions under which the FDA approved the exclusivity-protected drug for patient use, as reflected in the INDICATIONS AND USAGE section of the FDA-approved labeling." Pl.'s Opp'n at 7. Already, then, Braeburn has changed gears, strongly hinting at the phrase's uncertain meaning. Beyond that, Braeburn does not explain why the "Indications and Usage" section of a drug product's label is talismanic.

A third plausible reading is that "the conditions of approval" refers to "the particular circumstances that the FDA finds relevant to its determination that a drug should be approved for marketing, such as its method of delivery, the class of patients to whom it is to be delivered, or the nature of the chemical substance involved." Otsuka I, 302. F. Supp. 3d at 394. That interpretation has the virtue of linking "conditions" more closely to the FDA's "approval" determination, which in turn depends on investigations showing that the drug is safe and effective. 21 U.S.C. § 355(b)(1). From that angle, "the conditions of approval" might be each of

the drug product's characteristics or indications that, if changed, would render the drug unsafe, ineffective, or unfit for approval. Problematically for this interpretative route, the statute does not guide how to discern which conditions necessarily inform whether the FDA approves a new drug product. While establishing the safety and effectiveness of a drug's chemical substance and method of delivery in a certain class of patients might be essential to the FDA's approval decision, so, too, might the safety of a drug product's dosage form or strength or the effectiveness with which the drug minimizes negative side effects. Thus, even if construing "the conditions of approval" as the circumstances that inform the FDA decision is plausible, the statute does not compel this conclusion.

The structure of § 355(c)(3)(E)(iii) indicates a fourth approach to identifying which of the drug product's features are the "conditions of approval." As with other exclusivity-conferring provisions in the FDCA, § 355(c)(3)(E)(iii) operates through complementary clauses. In a regulation not challenged here, the FDA has interpreted the phrase "new clinical investigation" in the eligibility clause to mean investigations that produce results "which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product." 21 C.F.R. § 314.108(a). Eligibility for exclusivity, then, is the result of scientific breakthrough demonstrating the effective, safe use of a drug product for a new indication or in a new patient population. If "[t]he FDCA sets up a 'logical relationship between the change in the product for which the new clinical investigations were essential to approval of the [new drug application], and the scope of any resulting three-year exclusivity,'" see Veloxis, 109 F. Supp. 3d at 120–21

(quoting AstraZeneca Pharms. LP v. FDA, 872 F. Supp. 2d 60, 80 (D.D.C. 2012)), then harmonizing the two clauses might mean interpreting "the conditions of approval" as tied to the specific characteristics of the drug that warranted exclusivity in the first instance. In short, "the conditions of approval" would be the novel indications or patient populations for which the drug product may be used. That interpretation has the added benefit of serving the Hatch-Waxman Amendments' objective of finding an equilibrium that protects research and leaves room for market competition. On the other hand, separate exclusivity provisions in the FDCA bar subsequent approval "of an application submitted . . . for a change approved in" a previously-approved supplemental application containing new clinical investigations. See, e.g., 21 U.S.C. § 355(c)(3)(E)(iv), (j)(5)(F)(iv). The phrase "a change approved in" does not appear in § 355(c)(3)(E)(iii), but more strongly signals that the scope of exclusivity should be regarded in reference to novel features of a drug product that begot exclusivity in the first instance. If § 355(c)(3)(E)(iii) unambiguously was intended to work the same way, the bar clause more likely would have used language that specifically referenced the changes documented in the new clinical investigations, as was done in provisions conferring exclusivity to supplemental applications.

All of this is to say that while Braeburn and the FDA agree that "the conditions of approval" refers in some way to the protected drug product's characteristics, how to determine the subset of characteristics that matters for purposes of exclusivity is ambiguous. Therefore, Step One is not the end of the line.

**2. Chevron Step Two**

Section 355(c)(3)(E)(iii)'s ambiguity is not a license for the FDA to adopt any interpretation it chooses. The FDA's interpretation of "the conditions of approval" survives Step Two only if the agency reasonably construed the statutory language, a standard that the agency

can fail. Kisor, 139 S. Ct. at 2416. To satisfy Chevron's second inquiry, an agency must give a reasonable explanation for how its interpretation serves the statute. Mako Commc'ns, LLC v. FCC, 835 F.3d 146, 150 (D.C. Cir. 2016). "The analysis of disputed agency action under Chevron Step Two and arbitrary and capricious review is often 'the same, because under Chevron Step Two, [the court asks] whether an agency interpretation is arbitrary or capricious in substance.'" Agape Church, Inc. v. FCC, 738 F.3d 397, 410 (D.C. Cir. 2013) (quoting Judulang v. Holder, 565 U.S. 42, 52 n.7 (2011)). "[T]here are cases where an agency's failure to state its reasoning or to adopt an intelligible decisional standard is so glaring that we can declare with confidence that the agency action was arbitrary and capricious." Select Specialty Hosp.-Bloomington, Inc. v. Burwell, 757 F.3d 308, 312 (D.C. Cir. 2014).

As the Letter Decision articulates, the agency interprets "the conditions of approval" as found in § 355(c)(3)(E)(iii)'s bar clause to limit exclusivity to instances in which a follow-on drug product shares the "innovation" supported by the first product's "new clinical investigations essential to approval." AR 416 (sealed). In other words, a follow-on drug product cannot be approved within three years of the first product's approval, no matter the two products' differences, if the latter product incorporates the first's innovative features. AR 429 (sealed). To determine a drug product's innovative features, the FDA compares what changes an exclusivity-eligible drug product has made relative to any drug products previously approved to administer the same active moiety or moieties. AR 417 (sealed).

The FDA's interpretation most resembles the fourth of the plausible interpretations described in Section III.B.1, supra, identifying "the conditions of approval" as the subset of a drug product's features that entitle the drug to exclusivity. Yet, the Letter Decision gives short shrift to how the FDA arrived at its chosen statutory construction. The agency starts by

recognizing that the FDCA does not define "the conditions of approval," and, further, that the agency has not done so by regulation. AR 415 (sealed), 418 (sealed). From there, the FDA defends its construction as consistent with Congressional intent because "legislative history indicates that Congress intended 3-year exclusivity to protect only innovations that required the support of new clinical investigations essential to approval." AR 417 (sealed); see also AR 576 (54 Fed. Reg. at 28,896) (citing Congress's intention to award drug sponsor's with exclusivity only for significant developments). Defining "the conditions of approval" to protect an exclusivity-eligible drug product's innovative features "strikes a balance between rewarding innovation and increasing access as Congress intended." AR 429 (sealed). Cognizant of the peril of the first plausible interpretation described in Section III.B.1, supra, the Letter Decision explains that "the conditions of approval" cannot mean all the circumstances under which a drug product has been approved or modest changes to a drug product might save it from another's right to exclusivity, and render the right to exclusivity "virtually meaningless." AR 429 (sealed).

In the abstract, identifying "the conditions of approval" as the features of the drug that the clinical investigations essential to approval showed, for the first time, to be safe and effective—in other words, a drug's innovative features—respects the relationship between § 355(c)(3)(E)(iii)'s complementary clauses, Congress's intent, and is a first step toward filling the statutory ambiguity. In practice, however, describing a feature as an "innovation" risks becoming an empty label if the agency lacks a standard by which innovation is determined. To that end, the FDA adequately explains when a drug product's characteristics are not innovative, namely: if the characteristic already has been proved safe and effective in conjunction with a prior drug application. AR 417 (sealed). Yet, that definition is incomplete as it provides only a threshold for a characteristic to be deemed innovative. If exclusivity under § 355(c)(3)(E)(iii)

protects innovation, the FDA needs a rationale, based in the statute, to define the boundaries of a drug product's innovation. On that front, the agency advances no principle—legal or scientific—that guides its determination. Without any intelligible decisional principle for identifying innovation, the FDA's standard simply supplants the ambiguous phrase "the conditions of approval" for the ambiguous term "innovation."

To see the FDA's innovation standard in action illuminates how this really is no standard at all. For Sublocade, the FDA began its exclusivity analysis by reciting how Sublocade is not novel relative to previous buprenorphine drug products. AR 420–21 (sealed). Focusing on Sublocade's essential clinical studies, the FDA then concluded that Sublocade was the first product demonstrated to safely and effectively treat moderate-to-severe OUD through a monthly buprenorphine depot. AR 421 (sealed). Thus, Sublocade's innovation was a "monthly depot product that delivered an appropriate amount of buprenorphine over a one-month period to treat moderate to severe OUD." AR 421 (sealed).

Based on a review of the essential clinical studies, the FDA understood Sublocade's innovation as circumscribed both in terms of the dosing interval and severity of disease to be treated. Yet, in the next paragraph of the Letter Decision the FDA appreciates additional ways in which the same studies were limited: Sublocade is available only "to patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days" and is approved only for 300mg and 100mg doses. AR 421 (sealed). Still, the FDA dismissed these clinical study limits in defining the scope of the "innovation" and related exclusivity, stating, "Sublocade's exclusivity is not constrained by the use of the specific treatment initiation or dose adjustment schedule, or to the strengths for which it is approved . . . because the scope of an application's exclusivity covers the innovative change that is supported

by the new clinical investigation." AR 421–22 (sealed). For reasons the FDA claimed already to have given, "Sublocade's innovation, for which it received exclusivity, was that the dosing interval provided by the monthly depot product delivered an appropriate amount of buprenorphine over a one-month period to treat moderate to severe OUD." AR 422 (sealed). Sublocade's specific treatment regime, including the required dose-initiation schedule and dosing strengths, the FDA explained, did not limit that Sublocade treats OUD through a monthly buprenorphine depot and "[t]o determine that the scope of exclusivity encompassed those aspects would interpret Sublocade's exclusivity more narrowly than the scope of its innovation." AR 422 (sealed).

The FDA's statements, however, leave the most important question unanswered: what standard—legal or scientific—has the FDA applied to define Sublocade's innovation in the broad manner set forth in the Letter Decision? Why is dosing interval a way in which Sublocade's innovation is limited, but the drug product's high-loading dose of 300mg, the patient population on which it was tested, or other details of its specific treatment regime, are not? Leaving questions like that unexplored is especially pertinent given that both the FDCA and the FDA appreciate that drugs' characteristics may differ in multiple important dimensions. See 21 U.S.C. § 355(j)(2)(A)(iii) (making approval of an abbreviated new drug application contingent upon the drug sponsor showing "that the route of administration, the dosage form, and the strength of the new drug are the same as those of" an already-approved drug); AR 579 (54 Fed. Reg. at 28,899) (explaining that under 21 U.S.C. § 355(c)(3)(E)(iv)'s exclusivity provision "changes in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration or conditions of use would be granted exclusivity"). Additionally, under the FDA's definition of "new clinical investigation," a drug sponsor establishes a right to

exclusivity by conducting studies showing, for the first time, a drug product's safety for use in a new patient population. 21 C.F.R. § 314.108(a). At a minimum, then, patient population seems to be a critical dimension for defining the scope of the "innovation" and related exclusivity. To say, as the FDA has, that differences between the strength of Sublocade and a second drug, or differences in the patient population to which Sublocade and a second drug are available, for example, cannot be considered without infringing Sublocade's innovation is self-referential.

Rather than identifying a principle that guides how to conceive the limits of a drug product's innovation, the agency instead, at least here, defined innovation in the broadest possible sense. See Defs.' Reply at 13. An example, taken from Braeburn, see Pl.'s Mem. at 27–28; Pl.'s Opp'n at 17–18, illustrates the unreasonableness of that approach. Imagine that the FDA approves an application for a new drug product that is supported by an essential clinical investigation documenting, for the first time, the safety and effectiveness of a drug that administers buprenorphine in a monthly depot formula as a treatment for patients with OUD. All participants in the underlying essential clinical study, however, were men, leaving the drug product unapproved as a treatment for women. Under the FDA's approach, the relevant innovation would be defined as a monthly buprenorphine depot to treat OUD, rather than a monthly buprenorphine depot to treat OUD in men. As a consequence of defining the innovation in such a fashion, the exclusivity-eligible drug product bars approval of a subsequent monthly buprenorphine product shown to be an effective treatment for a patient population that the first drug does not reach, i.e., women.

The FDA's response is that the second drug, which showed for the first time the safety and effectiveness of administering a monthly buprenorphine depot to women, would be entitled to its own three-year period of exclusivity for that innovation but only when free from the first-

drug's exclusivity. AR 417 (sealed); Defs.' Reply at 14 n.7. The same result would obtain, according to the FDA, if Braeburn had, for example, demonstrated that Brixadi Monthly could be used without any titration period. Rough Tr. (July 15, 2019) at 55:7–16. Still, for the three-years that the initial drug product's exclusivity is effective, that exclusivity right keeps from the market a product that can serve an entirely distinct patient population or can be administered in a setting in which the first product categorically is unavailable. The disincentive for new innovations to expand available treatment options for new patient populations is obvious and appears to run counter to the over-arching goal of the Hatch-Waxman Amendments. The FDA does not answer how defining conditions of approval in a manner permitting those outcomes is reasonable. For a statutory construction, such as the FDA's, which identified only Congressional intent for support, those outcomes are tough to accept without any reasoned analysis.

Indivior and the FDA each fall back on characterizing the agency's definition of innovation as a scientific judgment entitled to special deference. See Defs.' Mem. Supp. Cross-Mot. Summ. J. & Opp'n Pl.'s Mot. Summ. J. ("Defs.' Mem.") at 27, ECF No. 28-1 (citing Serono Labs., Inc. v. Shalala, 158 F.3d 1313, 1320 (D.C. Cir. 1998); Intervenor-Def.'s Mem. at 41 (same). Certainly, in the process of determining when one drug product's exclusivity bars another drug's final approval the FDA exercises a degree of scientific judgment to draw proper lines. Indeed, parts of the Letter Decision suggest when that expertise is appropriately dispatched. For example, the FDA described certain elements of Brixadi Monthly as not "meaningfully different" from those of Sublocade. AR 427 (sealed); see also AR 429 n.89 (sealed) ("[W]e do not agree with many of the arguments Braeburn made regarding the clinical significance of differences between the two products."); AR 430 (sealed) (calling differences between Sublocade and Brixadi Monthly not "meaningful distinctions"). Yet, before the stage at

which the FDA determines that differences between two drug products are not "meaningful" for purposes of exclusivity, the FDA must explain the standard, consistent with § 355(c)(3)(E)(iii), that informs how the innovation against which those difference are judged is defined. As it stands, the FDA's judgment about whether Sublocade and Brixadi Monthly are meaningfully different was made against the backdrop of an approach to defining Sublocade's innovation that lacked substantive guideposts, and, consequently, against a possibly overly narrow vision of what "differences are relevant for purposes of this analysis." AR 429 (sealed). Once the FDA made its unguided decision that Sublocade's innovation was a monthly depot to treat moderate-to-severe OUD, any other difference was necessarily irrelevant, even if those differences make Brixadi Monthly available to a patient population, for example, that Sublocade is not.

Indivior also argues, Intervenor-Def.'s Mem. at 29; Intervenor-Def.'s Reply at 16, that the FDA's long-standing interpretation of § 355(c)(3)(E)(iii) should be presumed reasonable because Congress has not changed the relevant provisions of the FDCA since the FDA first adopted its interpretation, see Lorillard v. Pons, 434 U.S. 575, 580 (1978) ("Congress is presumed to be aware of an administrative or judicial interpretation of a statute and to adopt that interpretation when it re-enacts a statute without change."). The Lorillard presumption does not salvage the FDA's decision here because, since the Hatch-Waxman Amendments, Congress has not re-enacted the FDCA wholesale or even the contested provision. See United States v. Blavatnik, 168 F. Supp. 3d 36, 49 (D.D.C. 2016) ("First, and foremost, Congress did not re-enact the Tunney Act as a whole and did not re-enact the provision containing the language at issue here."). Furthermore, Indivior does not point to any evidence that Congress has considered the FDA's interpretation of "the conditions of approval." See id. ("Nor does the Government point

to any evidence that Congress gave any consideration to the meaning of 'consent judgment' in § 5(b)").

In the end, the attributes that Braeburn believes take Brixadi Monthly outside the scope of Sublocade's innovation might not, in fact, do so. That possibility does not save the agency's decision. *Oglala Sioux Tribe v. U.S. Nuclear Regulatory Comm'n*, 896 F.3d 520, 535 (D.C. Cir. 2018) ("Because the [agency] order appealed here does not rely upon this reasoning, . . . neither can we."). Rather, to analyze properly whether Brixadi Monthly is "for the conditions of approval" of Sublocade, the FDA must first explain what separates the elements of the essential clinical investigations incorporated into the definition of a drug product's innovation from those that are irrelevant, and why the identified dividing line reasonably applies § 355(c)(3)(E)(iii).

At bottom, interpreting "the conditions of approval" in § 355(c)(3)(E)(iii) in a manner that harmonizes that provision's eligibility and bar clauses is a reasonable first step. By starting from that point, the FDA has construed "the conditions of approval" that two drugs must share for one drug's right to exclusivity to bar final approval of a follow-on drug as the exclusivity-eligible drug's innovation. The flaw in the FDA's approach is to fail to supply a standard by which a drug's innovation is defined. Without such a standard, the FDA has not reasonably interpreted the statute and the Letter Decision must be vacated.

### C. The FDA's Award of Exclusivity to Sublocade

Even if the FDA's innovation standard reasonably interpreted § 355(c)(3)(E)(iii), Braeburn argues that the agency's application of that standard to Brixadi Monthly was arbitrary and capricious because the Letter Decision was plagued by inconsistency with respect to both the treatment of another buprenorphine product and prior applications of the same standard for different products. Pl.'s Mem. at 33. In each case, the alleged inconsistency is that the FDA failed to limit the scope of Sublocade's innovation by the patient population on which the drug

product was tested, as was done elsewhere. Braeburn is right as to each inconsistency, each of which is, in fact, a symptom of the FDA's unreasonable statutory interpretation discussed in the prior section.

### 1. *Letter Decision's* Inconsistent Treatment of Buprenorphine Products

To survive the judicial scrutiny that the APA requires, an "agency decision itself must be 'reasonable and reasonably explained.'" ANR Storage Co. v. FERC, 904 F.3d 1020, 1024 (D.C. Cir. 2018) (quoting Nw. Corp. v. FERC, 884 F.3d 1176, 1179 (D.C. Cir. 2018)). Agency action fails that standard if it exhibits internally inconsistent reasoning. Id. "Agency action is also arbitrary and capricious if it 'offered insufficient reasons for treating similar situations differently.'" Cal. Cmtys. Against Toxics, 2019 WL 2750852, at *9 (quoting Transactive Corp. v. United States, 91 F.3d 232, 237 (D.C. Cir. 1996)).

Here, Braeburn regards the FDA's assessment of Probuphine's innovation as incompatible with the corresponding assessment for Sublocade and, as a result, the exclusivity decisions as inconsistent. Pl.'s Mem. at 34–37. For Probuphine, the FDA limited the drug's defined innovation, in part, based on the patient population participating in the essential clinical investigation. Specifically, while "Probuphine was the first buprenorphine product to deliver buprenorphine via a subdermal implant," the approved dose was shown "to be effective for the treatment of opioid dependence only for a limited population of certain stable patients, so the scope of approval limited to such patients and therefore, the innovative change represented by Probuphine relates to the use of buprenorphine in that dosage form for that indication." AR 419 (sealed). Accordingly, "the conditions of approval" that defined the scope of exclusivity were "[1] a single-entity buprenorphine [2] subdermal implant product [3] for a 6-month period, [4] for the maintenance treatment of opioid dependence [5] in patients who have achieved and sustained prolonged clinical stability [6] on low-to-moderate doses of a transmucosal

buprenorphine containing product." AR 420 (sealed). Brixadi Monthly was not barred by Probuphine because the drug product did not share at least four of those criteria. Specifically, Brixadi Monthly was not a "6-month subdermal implant, but rather, for weekly and monthly depot injections of buprenorphine" and was "not limited to patients who have been stable on a low to moderate dose of buprenorphine for multiple months." AR 420 (sealed).

As with Probuphine, Sublocade was tested only on an identified patient population: new-to-treatment OUD patients "who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days." AR 421 (sealed); see also AR 14 (explaining that during Sublocade's development, Indivior had expressly elected to study its drug product in patient new to treatment).[11] Consistent with that approach, Sublocade was approved only for new patients who have undergone "dose adjustment for a minimum of 7 days." AR 97.[12] Nevertheless, Sublocade's innovation was not defined as limited by the patient group on which the drug was tested.

The FDA acknowledged in the Letter Decision that Sublocade was tested on a specific patient population, and that Braeburn sought approval for both "the induction and stabilization of patients that are new to buprenorphine treatment, as well as maintenance treatment for patients already receiving buprenorphine." AR 428 (sealed). Nonetheless, the agency characterized that

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[11] The FDA treats new-to-treatment patients who are dose-stabilized as a unique patient population. See AR 71 (instructing Sublocade to conduct post-marketing studies to develop a "greater understanding of how to transfer patients who are already clinically stable (vs. new entrants to treatment who are briefly dose-stabilized) onto Sublocade"); see also AR 432 (sealed) ("Despite Braeburn's argument to the contrary, the labeling for Sublocade does not require 'stabilization' in the sense of clinical stabilization, which can take months and would define a different population ('stable patients'). Instead, it requires a brief (several day) titration to a stable dose of sublingual buprenorphine meant to ensure that the patient can tolerate the 300mg dose.").

[12] Braeburn correctly observes, Pl.'s Mem. at 45 n.8, that the "Highlights" section of Sublocade's prescribing information directs treatment providers to "[v]erify that patient is clinically stable on transmucosal buprenorphine before injecting Sublocade." AR 95 (emphasis added). That summary, however, cross-references Section 5.11 of Sublocade's prescribing information which, in contrast, directs treatment providers to "[v]erify that patients have tolerated and are dose adjusted on transmucosal buprenorphine before subcutaneously injective Sublocade." AR 106 (emphasis added).

difference as irrelevant to exclusivity because Brixadi Monthly shared Sublocade's exclusivity-protected innovation: a product that "deliver[s] buprenorphine via a depot dosage form over a monthly period to treat moderate to severe OUD." AR 430 (sealed). That, however, does not answer why Sublocade's innovation had not been defined differently to account for the patient populations to which the drug could, and could not, safely be administered. By contrast, the patient population studied in Probuphine's clinical investigation was adopted into the statement of that drug product's innovation, and as a consequence narrowed the reach of Probuphine's exclusivity.

In their respective briefs, the FDA and Indivior each argues that the agency's approach to exclusivity for Sublocade was consistent with that of Probuphine. Probuphine did not bar Brixadi Monthly because that drug product was not a "six-month subdermal implant[] to treat patients stable on low-to-moderate doses of buprenorphine for many months." Defs.' Mem. at 33; see also Intervenor-Def's Reply at 24 ("Because Probuphine's studies thus supported a distinct product type (subdermal implant) for OUD patients with needs that are clinically distinct from those for whom Brixadi is appropriate (i.e., stable OUD patients needing only low-dose maintenance treatment v. patients experiencing moderate to severe OUD that requires high-dose treatment), FDA held that Probuphine's exclusivity didn't block Brixadi's approval."). Sublocade did bar Brixadi Monthly because each is a "monthly depot injection for the treatment of OUD." Defs.' Mem. at 34–35; see also Intervenor-Def.'s Reply at 24 ("Because Sublocade's studies thus supported the same type of product (injectable depot) for OUD patients with the same clinical needs as those for whom monthly Brixadi is appropriate (again, patients with moderate to severe OUD that requires high-dose buprenorphine treatment), FDA found that Sublocade's exclusivity blocked monthly Brixadi's approval.").

Those answers miss the point, as neither addresses why the FDA defined one innovation as circumscribed by the patient population, but did not apply the same definitional limit for another. If the Letter Decision had been consistent, Sublocade's innovation might have been defined as something akin to "monthly depot injection for the treatment of OUD in new-to-treatment patients following one week of titration on oral buprenorphine." With that definition of innovation, the reach of Sublocade's exclusivity might have been different.

As a result, the agency's determination of whether the Brixadi Monthly was subject to a right of exclusivity belonging to Sublocade was arbitrary and capricious.[13] For this separate reason, the FDA's Letter Decision must be vacated.

**2. L*etter Decision's Inc*onsistency with Historical Agency Action**

Similarly, Braeburn argues that by failing to define Sublocade's innovation to account for the only patient population on which Sublocade was tested, the FDA deviated from a prior agency decision, but without acknowledging the change in direction. Pl.'s Mem. at 37–45. Historically, Braeburn believes, the FDA has identified the "'innovative change' in each particular case by focusing on the patient population at issue and the 'underlying new clinical

[13] After the FDA denied final approval to Brixadi Monthly, Braeburn sent a letter requesting that the FDA approve the monthly product just for "patients who are stable on a transmucosal buprenorphine product." See Decl. of Sarah K. Frederick Supp. Mot. Prelim. Inj., Ex. 9, Feb. 28, 2019 Ltr. from Sharon Hertz to Mike Derkacz ("Feb. 28, 2019 Ltr.") at 34, ECF No. 7-11 (referencing letter from Braeburn). Braeburn had drawn the same distinction before the FDA issued the Letter Decision. AR 468. In a letter not included in the administrative record, the FDA rejected Braeburn's proposal. See Feb. 28, 2019 Ltr. at 34–36. In that letter, the FDA, for the first time, rationalized why Probuphine's innovation was defined to cover only clinically stable patients, while Sublocade's innovation was not defined as limited to only new patients who have undergone dose stabilization. According to the agency, Sublocade's "studies in new patients can support indications for both new and stable patients" because "[n]ew entrants to treatment . . . are considered a more difficult-to-treat population than patients who are already clinically stable." Id. at 35. Even if the FDA's assumption that a patient clinically stable on a low-dose buprenorphine product can transition to Sublocade, which may require increasing the volume of buprenorphine the patient receives more than tenfold, AR 98 (showing that Sublocade comes in only 300mg and 100mg doses), without jeopardizing people's health, the FDA's tardy justification fails to save this aspect of the Letter Decision because agency action must be evaluated by "the reasons stated in the orders under review," not "the agency's post-hoc rationalizations," ANR Storage Co., 904 F.3d at 1024; see also Oglala Sioux Tribe, 896 F.3d at 535 ("Because the [agency] order appealed here does not rely upon this reasoning, . . . neither can we.").

investigations that were essential to the [drug's] approval.'" Id. at 38 (quoting AR 415–16 (sealed), 473). If Braeburn is correct, the Letter Decision is arbitrary and capricious, as agencies may not "depart[] from agency precedent without explanation." Ramaprakash v. FAA, 346 F.3d 1121, 1124 (D.C. Cir. 2003).

For support, Braeburn refers to the FDA's exclusivity determination for Astagraf XL.[14] Astagraf XL is a prophylaxis for organ rejection in kidney transplant patients. AR 951, 958. Astagraf XL's exclusivity, the FDA determined, was limited to using the active ingredient as a once-daily prophylaxis for organ rejection in a specific population of kidney transplant recipients (referred to as de novo patients), AR 980, because Astagraf XL's new clinical investigations studied only that patient population, AR 990. Accordingly, Astagraf XL's exclusivity blocked Envarsus XR, a subsequent drug that used the same active ingredient for transplant patients, as a once-daily treatment for de novo patients, AR 981, but did not block Envarsus XR as a once-daily treatment for a separate patient population (referred to as conversion patients), AR 988.

The Letter Decision confronted the Astagraf XL decision by explaining that the agency had "concluded that conversion use is a different 'condition of approval' from the de novo use for which Astagraf XL received exclusivity." AR 431 (sealed). For kidney transplants, a product that established its safety and effectiveness in de novo patients did not bar subsequent approval of the same drug for conversion patients because the two groups have different "inherent risks and goals." AR 431 (sealed). In contrast, the ways in which Braeburn suggested Brixadi Monthly is different from Sublocade "are not differences that cause the monthly depot product proposed in the Brixadi application to fall outside the conditions of approval for which Sublocade received exclusivity." AR 432 (sealed). Despite those differences, "Braeburn is still

[14] The FDA's assessment of Astagraf XL's exclusivity was at issue and reviewed in Veloxis Pharmaceuticals, Inc. v. FDA, 109 F. Supp. 3d 104 (D.D.C. 2015).

seeking approval of a monthly depot formulation that delivers an appropriate amount of buprenorphine to treat OUD." AR 432 (sealed). To substantiate that conclusion, the FDA referred to its earlier section defining Sublocade's innovation. AR 432 (sealed).

This treatment of Sublocade's exclusivity, Braeburn urges, failed to limit the scope of Sublocade's innovation by the patient population on which the drug was tested—in this case, patients who "initiated with at least seven days of oral buprenorphine treatment," Pl.'s Mem. at 39—as had been done by limiting Astagraf XL's innovation to de novo patients. In its brief, the FDA defends its consistency, commenting that the agency did not impose any specific patient population as a limit on Sublocade's innovation because the efficacy demonstrated in Sublocade's testing "was not limited to a particular patient population." Defs.' Mem. at 34–35 (citing AR 421–22 (sealed)). Yet, in the cited portion of the Letter Decision, the FDA simply declared that "the particular treatment initiation, dose adjustment schedule, or strength" tested in Sublocade's studies cannot limit the scope of exclusivity or Sublocade's exclusivity would be tailored "more narrowly than the scope of its innovation." AR 422 (sealed). That portion of the Letter Decision, however, does not answer why the FDA could define Astagraf XL's innovation as limited to de novo patients without improperly depriving its sponsor of the benefit of the underlying innovation but the same could not be done for Sublocade.

Indivior, for its part, tries to rebut Braeburn's assertion about the FDA's departure from precedent by arguing that Brixadi Monthly and Sublocade do not actually treat different patient populations. See Intervenor-Def.'s Mem. at 35–43; Intervenor-Def.'s Reply at 21–25. Braeburn disagrees. In its view, proper line-drawing would permit final approval of Brixadi Monthly because that product "does not require take-home transmucosal buprenorphine for outpatient use" prior to the first monthly injection, Pl.'s Mem. at 41–42, and because Braeburn has

established, for the first time, the safety of efficacy of administering a monthly buprenorphine treatment to clinically stable OUD patients, id. at 43.

Whether Indivior or Braeburn is right, how Brixadi Monthly differs from Sublocade is an inquiry separate from the scope of Sublocade's innovation. Sure enough, the FDA's reply brief explains that "[t]he patient populations included in the Brixadi clinical studies have no bearing on the scope of the new clinical investigations essential to *Sublocade's* approval." Defs.' Reply at 22 (emphasis in original). Whether Sublocade's innovation still would block Brixadi Monthly if the agency had applied its innovation standard consistent with precedent is up to the agency to decide in the first instance. Still, the possibility of that decision leading to the same end point does not absolve the FDA from consistently applying its interpretation of § 355(c)(3)(E)(iii).

For this final reason, the Letter Decision must be vacated.

## IV. CONCLUSION

For the foregoing reasons, Braeburn's Motion for a Preliminary Injunction, ECF No. 7, is DENIED as moot and its Motion for Summary Judgment, ECF No. 24, is GRANTED; Indivior's Cross-Motion for Summary Judgment, or in the Alternative, Entry of a Stay, ECF No. 26, is DENIED; and the FDA's Cross-Motion for Summary Judgment, ECF No. 28, is DENIED.

This case is remanded to the FDA to reconsider, with deliberate speed, Braeburn's application for final approval of Brixadi Monthly.

An Order consistent with this Memorandum Opinion will be contemporaneously entered.

**Date**: July 22, 2019

BERYL A. HOWELL
Chief Judge