IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

BRAEBURN INC.,

Plaintiff,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, *et al.*,

Defendants,

INDIVIOR INC.,

Intervenor-Defendant.

No. 19-CV-982-BAH

PLAINTIFF BRAEBURN INC.'S MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF ITS MOTION FOR SUMMARY JUDGMENT

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GLOSSARY

ANDA	Abbreviated New Drug Application
APA	Administrative Procedure Act, 5 U.S.C. § 551 *et seq.*
FDA	U.S. Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*
NDA	New Drug Application

INTRODUCTION

Opioid use disorder, or OUD, "is a serious and life-threatening condition" that also results in "social and economic costs to society." FDA 4. The opioid epidemic is one of the greatest public health crises facing this country; more than two million Americans currently suffer from opioid-related substance-use disorders, and more than 400,000 people died from an opioid-related overdose between 1999 and 2017. FDA 158, 162; CENTERS FOR DISEASE CONTROL AND PREVENTION, *Opioid Overdose: Understanding the Epidemic* (Dec. 19, 2018), https://bit.ly/2jEOHfs. This case is about whether some OUD patients will be denied access to a new therapy that can serve their needs and thus improve public health, based on the supposed "exclusivity" of an existing product that cannot serve their needs. The correct answer is no: exclusivity is a limited reward for innovation resulting in a new FDA approval, and a product's exclusivity cannot extend beyond the uses and conditions for which the FDA has approved it.

Plaintiff Braeburn Inc. has developed a groundbreaking new treatment for OUD. Its drug product, Brixadi, is injected into a patient, forming a small mass called a "depot" that releases the active ingredient, buprenorphine, slowly and consistently over time. Brixadi has significant and potentially life-saving advantages over the predominant method of buprenorphine treatment—take-home, oral administration. Brixadi's administration by injection guarantees patient compliance during the treatment period and avoids the possibility that take-home oral buprenorphine will be misused or diverted, which can lead to overdoses and death. Indeed, a patient treated with Brixadi *never* needs to take home a single dose of oral buprenorphine.

The FDA has recognized that Brixadi's monthly formulation is safe and effective and has unique advantages that allow it to be used by patients for whom other buprenorphine depot products are not a viable treatment option. Yet the FDA refused to grant Brixadi final approval.

Instead, it decided that the three-year marketing exclusivity awarded to another drug product, Sublocade, blocks the approval of *any* other monthly buprenorphine depot product for the treatment of OUD—even though limitations on Sublocade's approval make it unavailable for many patients who *could* use Brixadi. The FDA's overbroad grant of exclusivity to Sublocade is contrary to the express terms of the Federal Food, Drug, and Cosmetic Act ("FDCA" or "Act"); violates the Administrative Procedure Act ("APA"); and undermines public health by depriving many patients of *any* access to a potentially life-saving therapy.

First, the FDA disregarded the express statutory limitation on the relevant form of exclusivity, which extends only to the "conditions of approval" of a drug. 21 U.S.C. § 355(c)(3)(E)(iii). Here, the FDA's exclusivity determination completely ignores a critical "condition" on Sublocade's "approval"—a condition established in the most important parts of Sublocade's FDA-approved label. Specifically, the FDA approved Sublocade for use *only* in patients who have undergone a period of initial treatment and dose adjustment with take-home, oral buprenorphine for a minimum of seven days. That limitation is necessary because of Sublocade's unusual formulation, which requires an extremely high "loading" dose that can cause serious adverse events if patients are not first started on take-home oral buprenorphine and "dose-adjusted" for at least a week. But the seven-day oral initiation period undermines one of the primary benefits of depot products, which is to avoid the significant risks (including drug overdose and death) associated with take-home oral buprenorphine. And it means Sublocade is unavailable for any patients who cannot tolerate or complete the seven-day initiation period that Sublocade's formulation requires. Indeed, a quarter of the patients enrolled in the clinical study supporting Sublocade's approval were never able to access Sublocade because they did not complete the study's required seven-to-fourteen days of oral buprenorphine treatment.

Brixadi could serve those patients, because its "conditions of approval" do not include any similar limitation. A doctor can administer Brixadi at the patient's first appointment without the need for any multi-day dose-adjustment period with take-home oral buprenorphine. This difference is meaningful because, as the FDA has explained, it "contribute[s] to better treatment adherence," allows use of Brixadi in settings where dose adjustment is not feasible (*e.g.*, "in emergency room settings"), and eliminates the need for *any* take-home oral buprenorphine, which "[r]educes [the] potential for diversion, misuse, abuse and accidental pediatric exposure." FDA 157, 158, 220. Under the statute's plain terms, Sublocade's exclusivity cannot extend beyond its "conditions of approval" to block other products lacking those conditions.

Second, the FDA's exclusivity determination is arbitrary and capricious. The decision itself is internally inconsistent. The FDA concluded that express conditions in Sublocade's label are not "conditions of approval" and therefore do not circumscribe the scope of its exclusivity. In the same breath, however, the agency concluded that express conditions in the label of another buprenorphine drug, Probuphine, *are* "conditions of approval" that *do* circumscribe the scope of its exclusivity. These determinations are irreconcilable. The FDA's decision, moreover, departs from the agency's longstanding interpretation of the FDCA. The FDA has consistently recognized that a drug's exclusivity cannot extend beyond the contributions of the "new clinical investigations" that were essential to the drug's approval. Here, however, Sublocade was not studied or demonstrated to be safe and effective *in all patients*; more specifically, its essential new clinical investigations included only patients who were new to treatment, and did not study patients who were already clinically stable on another form of buprenorphine treatment and transitioning to a monthly depot product. This again contrasts with Brixadi, which was studied in—and has been demonstrated to be safe and effective for—both new-to-treatment and

clinically stable, transitioning patients. By granting exclusivity beyond the scope of Sublocade's innovation and the contribution of the clinical studies necessary for its approval, the FDA contradicted its past interpretation of the statute.

For either of these reasons, Braeburn is entitled to summary judgment, and this Court should set aside the FDA's unlawful action.

BACKGROUND

I. Statutory and regulatory framework.

Before the FDA approves a new drug product, the product's sponsor must prove that it is effective and safe for use. *See* 21 U.S.C. § 355(d)(2); *see generally id.* § 355(a). To make that showing, the sponsor must submit one of three types of drug applications: a full New Drug Application ("NDA") under section 505(b)(1) of the FDCA, 21 U.S.C. § 355(b)(1); an Abbreviated New Drug Application ("ANDA") under section 505(j), 21 U.S.C. § 355(j), which seeks approval of a generic version of a drug product that the FDA has previously approved; or the type of application relevant here, an intermediate form of NDA under section 505(b)(2), 21 U.S.C. § 355(b)(2).

"Like the full NDA, a [section] 505(b)(2) NDA must directly demonstrate that the proposed drug product is safe and effective . . . ." *Veloxis Pharm., Inc. v. FDA*, 109 F. Supp. 3d 104, 108 (D.D.C. 2015). But to do so, the section 505(b)(2) NDA "can rely on clinical studies that were previously submitted to the FDA in support of another drug and that were not conducted or licensed by the [section] 505(b)(2) sponsor." *Id.* at 109 (brackets omitted); *see* 21 U.S.C. § 355(b)(2). Thus, unlike a generic ANDA, a section 505(b)(2) application contains full reports of clinical studies demonstrating the safety and effectiveness of the proposed new drug product, and unlike a full NDA, the section 505(b)(2) application relies, in whole or in part, on

safety and/or efficacy data from a previously approved drug product or products. Drug sponsors can submit an NDA under section 505(b)(2) when, for example, they seek approval for a new method of administration of an active ingredient that has been previously approved in another drug product or when they seek to extend the approval of an existing drug to a new patient population.

In certain circumstances, the Act gives a three-year period of marketing exclusivity to drugs approved under section 505(b)(1) or (b)(2) based on "new clinical investigations." If a drug qualifies for exclusivity, the FDA may not approve closely related drugs during that three-year period. The relevant provision states:

> If an application submitted under [section 505(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 [section 505(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 [section 505(b)] for the conditions of approval of such drug in the approved [section 505(b)] application effective before the expiration of three years from the date of the approval of the application under [section 505(b)] if [the application follows the 505(b)(2) pathway by relying on studies conducted by others].

21 U.S.C. § 355(c)(3)(E)(iii); *see id.* § 355(j)(5)(F)(iii) (same exclusivity also blocks approval of ANDAs for the same three-year period).

As this Court has recognized, this "new clinical trial" exclusivity is carefully calibrated to "strike a balance" between incentivizing innovative research and ensuring that patients have access to the drugs they need. *Veloxis*, 109 F. Supp. 3d at 107 (quotation marks omitted). On the one hand, the statute creates a relatively broad entitlement to *some* exclusivity: a product qualifies if (1) it "includes an active ingredient . . . that has been approved in another [(b)(1) or (b)(2) NDA]"; and (2) the application for the drug "contains reports of new clinical

investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." 21 U.S.C. § 355(c)(3)(E)(iii); *see also* 21 C.F.R. § 314.108(b)(4). On the other hand, the same provision strictly limits the *scope* of that new clinical trial exclusivity, tying it to—and constraining it by—the drug product's "conditions of approval." 21 U.S.C. § 355(c)(3)(E)(iii); *see also* 21 C.F.R. § 314.108(b)(4); FDA 415 (exclusivity provides "limited protection" from competition). For instance, if the "conditions of approval" of a first-approved drug restrict the use of that drug to a particular indication or type of patient, then that drug's exclusivity does not bar approval of another drug that is shown to be safe and effective for *other* indications or *other* patients, even if that second-approved drug product shares other characteristics with the first-approved drug product. *See Veloxis*, 109 F. Supp. 3d at 117 (explaining that exclusivity is "triggered by an overlap in the *conditions of approval* between the first-in-time 505(b) drug and the second-in-time 505(b)(2) NDA"). This limitation is vital to ensure that the exclusivity does not deprive a group of patients of access to *any* safe and effective drug.

Consistent with this statutory text, the FDA has repeatedly explained that the use of the phrase "conditions of approval" in section 355(c)(3)(E)(iii) imposes two independent constraints on a drug's exclusivity: exclusivity may not extend beyond either (1) the "scope of the [agency's] approval" or (2) the scope of the "new clinical investigations" that formed the basis for that approval. FDA 1026; *see also* FDA 1386, 1500, 1659, 1665-66, 1785, 1793 (same). More specifically, the FDA has interpreted the statutory phrase "conditions of approval" to mean the "innovative change that is supported by the new clinical investigations" that entitled the drug product to approval. FDA 1025; *see also* FDA 1389, 1500, 1665, 1792-93 (same). And the agency has clarified that a product's "innovative change" is "circumscribed by the scope of the

'new clinical investigations' essential to the approval of the change." FDA 1027-28; *see also* FDA 1390, 1501 (same). In this way, the FDA has recognized that any crucial limitations on the scope of a drug's approval—or even limitations on the scope of the *clinical investigations* that led to that approval—will likewise limit the scope of the drug's exclusivity.

Veloxis considered the FDA's application of these principles to the section 505(b)(2) NDA for the immunosuppressant Envarsus XR. As part of its approval process, the agency considered whether the new clinical trial exclusivity belonging to a previously approved drug product, Astagraf XL, barred the FDA from approving Envarsus. The agency concluded it did not: as the FDA explained, the scope of Astagraf's approval was limited based on the type of patients studied in the new clinical investigations essential to Astagraf's approval. Specifically, Astagraf's sponsor had examined that drug only "for the prophylaxis of organ rejection in *de novo* kidney transplant patients"—*i.e.*, patients who recently received a transplant and need to begin taking immunosuppressant drugs. FDA 1036; *see also Veloxis*, 109 F. Supp. 3d at 110 (describing "*de novo*" patients). Astagraf's sponsor "did not obtain approval of Astagraf in conversion patients"—*i.e.*, patients who are in the process of replacing one immunosuppressant drug with another. FDA 1043; *see also Veloxis*, 109 F. Supp. 3d at 110 (describing "conversion" patients). Because Astagraf had been studied only in *de novo* patients, the FDA reasoned, Astagraf's exclusivity could not "extend beyond" those *de novo* patients and could not block the agency from approving Envarsus for conversion patients. FDA 1043. In other words, because Astagraf's sponsor had not studied Astagraf in conversion patients, "the Agency concluded that the conversion use is a different 'condition of approval' from the *de novo* use for which Astagraf XL received exclusivity." FDA 1045.

II. The opioid crisis.

The nation is in the midst of a growing opioid epidemic. In 2015 alone, more than 12 million people misused prescription opioids and more than 33,000 people died from opioid drug overdoses. FDA 162. And these numbers are on the rise: in 2017, the number of opioid-related deaths was six times higher than in 1999. CENTERS FOR DISEASE CONTROL AND PREVENTION, *Opioid Overdose: Understanding the Epidemic* (Dec. 19, 2018), https://bit.ly/2jEOHfs. Recent data suggest that more than two million Americans currently suffer from opioid-related substance-use disorders. FDA 158, 162; *see also* NATIONAL INSTITUTE ON DRUG ABUSE, *Opioid Overdose Crisis*, https://bit.ly/2j6YEE1 (last updated Jan. 2019).

Recognizing that the crisis is escalating, the federal government has made addressing the opioid epidemic in America a top priority. In October 2017, the President declared the opioid crisis a Nationwide Public Health Emergency. WHITE HOUSE, Press Release, *President Donald J. Trump is Taking Action on Drug Addiction and the Opioid Crisis* (Oct. 26, 2017), https://bit.ly/2VBqPfU. That same month, officials from the U.S. Department of Health and Human Services ("HHS") and the FDA testified before Congress and reiterated the administration's commitment to addressing the crisis. *See* SENATE HEALTH, EDUCATION, LABOR AND PENSIONS COMMITTEE, *The Federal Response to the Opioid Crisis: Written Testimony on Behalf of Witnesses from HHS* (Oct. 5, 2017), https://bit.ly/2RHrPjv. As part of its five-point strategy to address the opioid epidemic, HHS has pledged to "[i]mprove access to prevention, treatment, and recovery support services to prevent the health, social, and economic consequences associated with opioid addiction and to enable individuals to achieve long-term recovery." HHS, *Strategy to Combat Opioid Abuse, Misuse, and Overdose*, at 3, https://bit.ly/2R5bhPv.

Consistent with that effort, then–FDA Commissioner Scott Gottlieb announced in September 2017 that medication-assisted treatment—*i.e.*, the use of medication in combination with counseling and behavioral therapy—"is one of the major pillars of the federal response to the opioid epidemic in this country." FDA, Press Release, *Statement from FDA Commissioner Scott Gottlieb, M.D., on the Agency's Continued Efforts to Promote the Safe Adoption of Medication-Assisted Treatment for Opioid Addiction* (Sept. 20, 2017), https://bit.ly/2D02WZr. During a House hearing on the federal response to the opioid epidemic, Dr. Gottlieb went even further, calling for the expanded use of medication-assisted treatment, and explaining that the FDA would issue new guidance to manufacturers to promote the development of novel therapies like depot products, which help to facilitate patient adherence. FDA, Press Release, *Remarks from FDA Commissioner Scott Gottlieb, M.D., as Prepared for Oral Testimony Before the House Committee on Energy and Commerce* (Oct. 25, 2017), https://bit.ly/2FjVxFp. FDA issued draft guidance in April 2018, FDA 1797-1806, and final guidance on February 6, 2019. *See* FDA, *Opioid Use Disorder: Developing Depot Buprenorphine Products for Treatment—Guidance for Industry* (Feb. 2019), https://bit.ly/2J4DaGk ("2019 OUD Guidance").

III. OUD treatment with buprenorphine.

One of the most common active chemical ingredients for treatment of OUD is buprenorphine. *See* FDA 4. The FDA first approved buprenorphine for medical use in 1981, and first approved a buprenorphine drug product to treat OUD in 2002. FDA 404. Buprenorphine "reliev[es] patients' urge to use illicit opioids." FDA 164. More specifically, buprenorphine "blocks [illicit opioid drugs] from achieving their full effects, deterring abuse of these substances for buprenorphine-maintained patients." *Id.*

The most prevalent form of buprenorphine treatment for OUD is daily oral (or

"transmucosal") administration of the drug, meaning a dosage form administered under the tongue or inside the cheek. *See* FDA 4. As the FDA itself has recognized, treatment with oral buprenorphine carries a number of significant risks, and oral buprenorphine is not appropriate or adequate for many people with OUD. For one thing, the success of an oral buprenorphine regimen depends on a patient's ability to "remember to take medication on a daily basis for long-term and even lifelong maintenance," FDA 1221, leading to problems of "poor adherence." FDA 4. Moreover, because oral administration requires patients to receive and keep a supply of buprenorphine—which is itself a Schedule III controlled substance—the product is prone to "diversion, misuse, [and] abuse." FDA 4; *see* FDA 104. Indeed, "[t]he most frequently reported systemic postmarketing adverse event observed with buprenorphine sublingual tablets [has been] drug misuse or abuse." FDA 111. Finally, the use of take-home oral buprenorphine has been known to result in "accidental pediatric exposure"—*i.e.*, unintentional contact with the drug by children—which "can cause severe, possibly fatal" slowing of children's breathing. FDA 4, 108, 456-57 nn. 14-15, 1220.

In light of these issues, the FDA has encouraged the development of "novel formulations or delivery mechanisms" of buprenorphine—such as "sustained-release depots and implants"—that allow "effective treatment for OUD" with "less misuse, abuse, or accidental exposure compared to self-administered formulations such as transmucosal tablets and films." FDA, *FDA Finalizes New Policy to Encourage Widespread Innovation and Development of New Buprenorphine Treatments for Opioid Use Disorder* (Feb. 6, 2018), https://bit.ly/2RJ5OwB. For example, the FDA granted "priority review" to the NDA for Probuphine, a six-month subdermal buprenorphine implant, in light of its potential to curb the diversion, abuse, and misuse associated with take-home oral buprenorphine. FDA 1396. In undertaking its clinical review of

Probuphine as part of the approval process, the FDA's Center for Drug Evaluation and Research ("CDER") highlighted again and again the risks inherent in oral buprenorphine treatment—and Probuphine's capacity, as an implantable product, to obviate those risks.[1] CDER ultimately determined that Probuphine was "not unacceptably less effective than" oral buprenorphine—*i.e.*, that it was, at worst, only somewhat less effective than oral buprenorphine—but emphasized that it offered important benefits such as "not needing to take medication on a daily basis for long-term and even lifelong use" and "reduced risk of accidental exposure for children who may be in the home," and stressed that it "reduce[d] the risk of misuse, abuse, and accidental pediatric exposure." FDA 1279. The FDA granted final approval to Probuphine in May 2016. FDA 404.

IV. The FDA's limited conditions of approval for Sublocade.

Indivior submitted a section 505(b)(2) NDA for Sublocade on May 30, 2017. FDA 1, 86. Like Brixadi, Sublocade is an injectable depot product, though its indication, injection site, formulation, available doses, and dosing recommendations are different. FDA 12. As with Probuphine, the FDA granted Sublocade "priority review" "[b]ecause of the potential for a depot product to mitigate risks of abuse, diversion, and accidental pediatric exposure associated with oral transmucosal buprenorphine." FDA 12. And as with Probuphine, the agency's clinical

[1] *See, e.g.*, FDA 1220 ("Transmucosal buprenorphine products increasingly have been targets of abuse, misuse, and diversion, and have been implicated in incidents of accidental pediatric exposure. Because it is implanted surgically, Probuphine is intended to be less vulnerable to these risks."); 1222-23 ("[F]or properly-selected patients, Probuphine offers an alternative to daily transmucosal buprenorphine treatment and is not unacceptably inferior to this treatment. The benefits to the patients, including convenience, privacy, and reduced, risk of theft or accidental exposure of household contacts are augmented by the potential benefits to public health of a reduced risk of misuse, abuse, diversion, and accidental pediatric exposure which are associated with transmucosal buprenorphine products. These benefits outweigh the potential risks of the product . . . ."); 1229 ("[Oral buprenorphine] drug products have been subject to abuse and misuse, and have been implicated in cases of accidental pediatric poisonings."); 1231 (noting "the public health benefit that Probuphine could potentially offer related to decreased misuse, abuse, and accidental pediatric exposure").

review of Sublocade repeatedly noted the risks associated with oral, take-home buprenorphine treatment—and the potential for Sublocade to decrease those risks.[2] The FDA approved the Sublocade NDA on November 30, 2017. FDA 406; *see* Sublocade Approval Letter (Nov. 30, 2017) (ECF No. 7-7).

Importantly, however, Sublocade's "conditions of approval" do not extend to all OUD patients. Rather, Sublocade's approval is limited in two relevant ways. First, Sublocade is only approved for OUD patients who were able to complete both an initiation and dose-adjustment period with take-home oral buprenorphine for a minimum of seven days. Second, Sublocade was only studied in—and therefore only demonstrated to be safe and effective for—a subset of OUD patients who are new to treatment.

A. Required initiation and dose adjustment with oral buprenorphine.

Sublocade's label is clear: the drug is approved only for patients who have initiated treatment, and completed at least seven days of dose adjustment, with oral buprenorphine. Indeed, this clinically important limitation is repeated several times throughout the principal sections of the label. The "INDICATAIONS AND USAGE" section states that Sublocade is approved specifically for OUD "patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days." FDA 97. The "Patient Selection" section of the label states that the patients who are

[2] *See, e.g.*, FDA 4 ("Oral-transmucosal buprenorphine and buprenorphine/naloxone products and oral naltrexone products are intended to be self-administered by the patient daily. Limitations of daily use products include poor adherence, fluctuating plasma concentrations, intentional 'drug holidays,' as well as patient convenience issues. Daily use agonist and partial agonist [medication-assisted treatment] products are subject to diversion, misuse, abuse, and accidental pediatric exposure."); 14 ("[B]uprenorphine sublingual products have been increasingly identified in the illicit drug market, and it is known that they are diverted, abused, and misused. Additionally, they have been implicated in a number of cases of accidental poisonings of small children. Therefore, a depot injection which would be difficult to divert or abuse, and would be less likely to be accidentally ingested by small children, offers potential advantages.").

"appropriate for SUBLOCADE are adults who have initiated treatment on a transmucosal buprenorphine-containing product delivering the equivalent of 8 to 24 mg of buprenorphine daily. *The patient may only be transitioned to SUBLOCADE after a minimum of 7 days*." FDA 98 (emphasis added). The "Highlights" section warns physicians to "[v]erify that [the] patient is clinically stable on transmucosal buprenorphine before injecting SUBLOCADE." FDA 95. And Sublocade's "Medication Guide" likewise specifies that Sublocade is approved for patients who "have received treatment with an oral transmucosal (used under the tongue or inside the cheek) buprenorphine-containing medicine for 7 days **and** are taking a dose that controls withdrawal symptoms for at least seven days." FDA 134 (emphasis in original). Notably, Indivior originally proposed a label *without* the seven-day period, stating only that Sublocade "is indicated for the treatment of moderate-to-severe opioid use disorder in patients *who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product*," but the Review Division recommended "modifying the language to reflect the fact that study participants had to be dose-stabilized for at least seven days before initiating Sublocade." FDA 67 (emphasis added).

As its prominence in Sublocade's label suggests, the requirement that a patient complete a seven-day period of dose adjustment with oral buprenorphine is no small matter; it was a necessary consequence of the limitations of Sublocade's particular formulation. The FDA acknowledged that there would be "great interest in initiating [depot] treatment . . . as rapidly as possible," and specifically in "accelerat[ing] . . . by omitting some or all of the [dose-adjustment] period." FDA 71. The FDA nonetheless imposed the seven-day limitation for Sublocade in light of the serious risks posed by Sublocade's unusual formulation, which requires an extremely high "loading" dose (300 mg) at the beginning of treatment. "[B]ecause the doses of buprenorphine

provided by Sublocade are higher than doses of [oral buprenorphine] typically used to initiate treatment," the agency explained in its clinical review, "there is a risk that precipitated withdrawal, a clinically serious condition, could occur if Sublocade is initiated without a period of [oral buprenorphine] titration." FDA 71. As the FDA further noted, Sublocade's "clinical trials included a significant period of dose run-in on transmucosal buprenorphine," and it is therefore "not known whether Sublocade could precipitate withdrawal if initiated in patients who have not had a period of transmucosal buprenorphine treatment." FDA 65; *see also* FDA 10 (same).

Sublocade's lack of approval in patients who have not initiated treatment and dose-adjusted with seven days of oral buprenorphine substantially limits the number of patients who may access the drug, because not all patients will be able to tolerate or complete the initiation/dose-adjustment process. Indeed, in one of the studies that was essential to Sublocade's approval, *nearly a quarter* of patients who began treatment with oral buprenorphine did not make it through the required seven-to-fourteen-day run-in period, and hence were not able to use Sublocade *at all*. FDA 56. Similarly, because Sublocade cannot be the first buprenorphine treatment a patient receives, it cannot be administered in certain clinical settings, like emergency rooms. *See* FDA 220.

The seven-day initiation/dose-adjustment limitation also creates its own safety concerns: requiring that patients use oral buprenorphine for seven days entails the very same risks involving compliance, abuse, diversion, and accidental pediatric poisoning that buprenorphine depot products were intended to avoid. *See supra*, p. 10. The FDA itself recognized as much, explaining that a depot injection that did not require initiation with oral buprenorphine "would contribute to safer use of the drug" by "increasing the likelihood of the patient adherence to

treatment from the outset, and reducing the need to provide take-home [oral buprenorphine] medication for outpatient use." FDA 71. Thus, as part of Indivior's "postmarketing requirements" under section 505(*o*) of the FDCA, the FDA has required Indivior to conduct a clinical trial exploring whether Sublocade can be safely initiated without a seven-day titration period on transmucosal buprenorphine. FDA 10-11; *see also* Sublocade Approval Letter, *supra*, at 5. That clinical study is not scheduled to be submitted to the FDA until August 2021. Sublocade Approval Letter, *supra*, at 5. So, even if these studies ultimately show that Sublocade can be safely administered without seven days of oral buprenorphine treatment—and there is no reason to think that these studies necessarily will reach that conclusion given Sublocade's unusual formulation and high loading dose—it will be close to three years before Sublocade could be available for patients who cannot complete at least a week of oral buprenorphine treatment.

B. New clinical investigations only in new-to-treatment patients.

As discussed, the FDA has consistently taken the position that a drug's "conditions of approval" are "circumscribed by the scope of the 'new clinical investigations' essential to the approval" of the drug. *Supra*, pp. 6-7. In the case of Sublocade, the FDA identified two "new clinical investigations" as "essential to approval of the NDA": (1) a "Blockade Study," also known as Study RB-US-13-0002, and (2) a "Pivotal Efficacy Study," also known as Study RB-US-13-0001. FDA 407. Both studies were limited to a subset of the OUD population: patients who were new to OUD treatment. *See id.* That is, neither investigation examined Sublocade in patients who were already stable on an established dose of oral buprenorphine. Notably, FDA guidance has recognized that patients new to OUD treatment and those already stable on other OUD treatments are distinct patient populations that should be studied separately. 2019 OUD

Guidance, *supra*, at 5.

The FDA expressly acknowledged the limited scope of Indivior's studies throughout its review and approval of Sublocade. For example, CDER's clinical review noted that the FDA and Indivior discussed the "options for [OUD] populations" for which Indivior could seek approval, described by the FDA as "new entrants to treatment vs. established, stable patients." FDA 14. "Indivior elected to study patients new to treatment," and the FDA agreed that this claim could be supported by the two primary studies Indivior ultimately conducted. FDA 14. The FDA concluded, however, that because of Sublocade's high "loading doses," more information was needed to determine how to safely "transfer patients who are already clinically stable (vs. new entrants to treatment who are briefly dose-stabilized) onto Sublocade." FDA 71. Likewise, the agency's approval letter confirmed that "SUBLOCADE was studied only in patients new to treatment"—as distinct from "patients who are already clinically stable and abstinent after a period of treatment with transmucosal buprenorphine." Sublocade Approval Letter, *supra*, at 6.

This limitation is also reflected in several aspects of Sublocade's approved label. In particular, the label is completely silent as to *how* a patient who is stable on a known dose of oral buprenorphine would transition to Sublocade. (That is in direct contrast to Brixadi's label, which provides a chart clearly explaining how to transition patients from doses of oral buprenorphine to doses of Brixadi. FDA 279-80.) Moreover, Sublocade's dosing instructions present significant hurdles for patients who are already stable on oral buprenorphine, particularly patients who are stable on a low dose. That is because, as mentioned, Sublocade's dosing regimen requires two initial loading doses of 300 mg per month, which is much higher than the long-term maintenance dose of 100 mg per month. *E.g.*, FDA 98, 103. As the FDA has explained, this dosing regimen

clearly limits Sublocade's utility to "patients new to treatment." Sublocade Approval Letter, *supra*, at 6. In express recognition of this limitation, the FDA reminded Indivior of its commitment to conduct an additional postmarketing study "to evaluate the transition of patients with long term stability on a transmucosal buprenorphine dose to a monthly dose of SUBLOCADE without the use of a loading dose." *Id.* at 7.

V. The FDA's approval of Brixadi without Sublocade's limitations.

Brixadi is an extended-release formulation of buprenorphine designed for administration by subcutaneous injection in ready-to-use prefilled syringes. Brixadi comprises both weekly and monthly formulations—with multiple doses for each offering—to fit the different needs of patients at different phases of their recovery. FDA 156. Weekly dosing may be advantageous for unstable patients who need more frequent clinic visits or use the product in conjunction with other forms of treatment such as psychological counseling. FDA 168; *see also* FDA 275 (noting that "BRIXADI should be used as part of a complete treatment program that includes counseling and psychosocial support"). In contrast, monthly dosing intervals may be more suitable for patients who are more stable and do not need weekly oversight. FDA 168. Brixadi has been successfully evaluated in seven Phase 1-3 clinical trials, including a pivotal Phase 3 efficacy study and a long-term safety study. FDA 170.

Braeburn submitted a section 505(b)(2) NDA for Brixadi on July 19, 2017—less than two months after Indivior submitted its NDA for Sublocade. FDA 270. Brixadi does not share two key elements of Sublocade that are part of Sublocade's "conditions of approval."

First, Brixadi does not require any extended initiation/dose-adjustment period with oral buprenorphine. Indeed, its clinical studies were designed to show that Brixadi "would be appropriate for use from the first patient visit . . . , so that no take-home use of sublingual

buprenorphine would be necessary in the real-world setting." FDA 194. The FDA highlighted the clinical importance of this innovation in its clinical review. In particular, the CDER memo emphasized that:

> [Braeburn] is . . . seeking approval for [Brixadi] for the *initiation* of OUD treatment, without the need for a lead-in period of [oral buprenorphine] before switching to the use of this product. . . . If approved, [Brixadi] would represent the first weekly and monthly, flexible-dosing, extended-release, [buprenorphine] product on the market to treat moderate to severe OUD. In addition, [Brixadi] would be the first extended-release [buprenorphine] product that can be administered to new entrants to [buprenorphine] treatment for this indication without an initial run-in on transmucosal buprenorphine.

FDA 152.

The agency expressly contrasted Sublocade. The CDER memo noted that Sublocade's "labeling requires at least a seven-day run-in period on transmucosal buprenorphine," FDA 158, and that one "benefit" of Brixadi is that it is "[d]esigned for the initiation of OUD treatment without a lead-in period on sublingual buprenorphine," FDA 159. As the agency explained:

> [T]he [Brixadi] regimen has the potential to provide several advantages, including less frequent dosing to achieve target dosing of [buprenorphine]; flexible dosing regimens; and the ability to receive [buprenorphine] without take-home medications, all of which may contribute to better treatment adherence.

FDA 157. "Additionally," the agency noted, "because [Brixadi] can be administered after a single test dose of transmucosal buprenorphine, this product has the potential to be used early on in [medication-assisted treatment] or, potentially, in emergency room settings where treatment can be initiated before the patient follows up with a provider. Thus, [Brixadi] could provide several clinical benefits for the treatment of OUD." FDA 220.

With Brixadi (unlike Sublocade), after patients take a single, small oral dose of buprenorphine in the doctor's office to ensure they tolerate buprenorphine, they can receive their first depot injection at their first appointment, without having ever undergone prior OUD

treatment. In Brixadi's clinical studies, less than one percent of patients did not tolerate buprenorphine, FDA 205 (compared with the one-quarter that did not complete Sublocade's run-in period, FDA 56). This ability to forgo a dose-adjustment period with take-home oral buprenorphine guarantees patient compliance from day one, allowing patients and the public to avoid the well-acknowledged risks and burdens associated with requiring patients to undergo treatment with take-home oral buprenorphine. *See* FDA 162, 164-65.

Second, also unlike Sublocade, Brixadi was studied in—and thus demonstrated to be safe and effective for—both new-to-treatment patients *and* patients who have achieved stability on another form of treatment. FDA 178-79. Brixadi is thus available for immediate use with a flexible dosage offering that can address *any* patient profile, including patients "who are already being treated with buprenorphine," FDA 277, rather than only a subset of new-to-treatment patients like Sublocade. For that reason, Brixadi lacks the limitations that make Sublocade inappropriate for patients converting from oral buprenorphine. Brixadi does not require an initial loading dose—*i.e.*, a higher, 300 mg dose during the first two months of depot treatment. And unlike Sublocade, Brixadi's label contains instructions for "Patients Switching from Transmucosal Buprenorphine-containing Products to BRIXADI," along with tables matching corresponding doses of oral buprenorphine to weekly and monthly Brixadi. FDA 278-80.

In short, Brixadi provides a highly valuable treatment option for patients who are not otherwise able to use depot products, including patients who cannot tolerate the high loading dose of Sublocade, high-risk patients for whom there is good reason to avoid any take-home administration of oral buprenorphine, patients who cannot tolerate at least seven days of oral buprenorphine, and patients who are not ready to begin treatment using a monthly depot product (rather than one with both weekly and monthly options) based on concerns about side effects,

durability, and long-term exposure.

VI. The FDA's exclusivity determination.

While both Brixadi and Sublocade were under review by the FDA, counsel for Braeburn submitted a letter to the FDA raising the issue of exclusivity pursuant to 21 U.S.C. § 355(c)(3)(E)(iii). *See* FDA 437-41. "The fact that two long-acting, injectable buprenorphine products are moving through FDA review process at the same time," the letter explained, "raises questions about how exclusivity will be assigned." FDA 438. Ultimately, the letter explained, "if [Sublocade] is approved before [Brixadi], the scope of [Sublocade]'s exclusivity would have legal limits—it would be limited both by the conditions of approval of previously approved buprenorphine products and by the design of [its] 'essential' clinical trials." FDA 440. Following the FDA's approval of Sublocade, counsel for Braeburn submitted follow-up letters to the agency regarding the scope of Sublocade's exclusivity. *See* FDA 442-72. The letters provided a detailed legal analysis regarding the potential scope of any new clinical trial exclusivity for Sublocade, and the reasons why that exclusivity would not block approval of Brixadi. In particular, and as relevant here, the letters explained that Brixadi does not share Sublocade's exclusivity-protected "conditions of approval," focusing in particular on (1) the requirement for a minimum seven-day run-in period with oral buprenorphine, which entails significant risks such as abuse, misuse, diversion, and accidental pediatric poisoning; and (2) the lack of any clinical data or labeling language to support transitioning long-term stable patients to a monthly depot product. *E.g.*, FDA 467-71.

The FDA "completed [its] review" and "tentatively approved" Braeburn's application on December 21, 2018. FDA 270. In other words, the FDA determined that Brixadi "otherwise meets the requirements for approval," but is blocked by "a period of exclusivity." 21 C.F.R.

§ 314.105(a) (explaining tentative approval); *see id.* § 314.108(b)(4); FDA 270. The FDA specified that "final approval of [Braeburn's] application under section 505(c)(3) of the Act may not be granted before the period has expired." FDA 270.

In a separate, two-page letter, also dated December 21, the agency further explained that the "3-year exclusivity for Sublocade blocks the approval of Brixadi with regard to its monthly depot product." FDA 473.[3] Sublocade's three-year exclusivity expires on November 30, 2020. FDA 403.

The letter reiterated the agency's understanding that "the scope of 3-year exclusivity under section 505(c)(3)(E)(iii) . . . cover[s] the 'innovative change' from previously approved drug products containing the same active moiety for which the underlying new clinical investigations were essential to the approval." FDA 473. "To determine the scope of exclusivity for Sublocade," the letter explained, the FDA had "reviewed the administrative record for the approval of the Sublocade NDA and the clinical investigations deemed to be essential to its approval in relation to prior approvals of buprenorphine products." *Id.* "Based on [that] analysis," the letter continued, the FDA had determined "that the scope of Sublocade's unexpired exclusivity is the use of a monthly depot product with buprenorphine as its active moiety that is indicated for treatment of moderate to severe opioid use disorder (OUD)." *Id.*

The reasoning underlying that exclusivity determination is found in a December 21, 2018 memorandum from the CDER Exclusivity Board. *See* FDA 402-36. There, the Board acknowledged that "Sublocade's approved indication is limited to patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days." FDA 421; *see also* FDA 406 (same). Nevertheless, the Board

[3] The agency opined that Brixadi's *weekly* formulation would not be blocked. FDA 474.

concluded that Sublocade's exclusivity was broader than the scope of its approval; it determined that Sublocade's exclusivity encompasses *all* monthly depot buprenorphine products—even depot products that do *not* require initiation and dose adjustment with oral buprenorphine.

In particular, the Board opined that "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." FDA 422, 427, 429. Thus, the agency "consider[s] Sublocade's approval for use of a monthly buprenorphine depot for the treatment of OUD"—without more—to constitute the relevant "innovative change" that grants exclusivity. FDA 421. Accordingly, the agency rejected the argument "that the scope of Sublocade's exclusivity is . . . constrained by the use of the specific treatment initiation or dose adjustment schedule" contained in Sublocade's label, including the INDICATIONS AND USAGE section. FDA 421-22. The agency's letter did not address at all one of the central issues raised in Braeburn's letters: the risks of abuse, misuse, diversion, and accidental pediatric poisoning posed by Sublocade's minimum seven-day initiation and dose-adjustment period with take-home oral buprenorphine.

The agency also brushed aside the possibility that Sublocade's exclusivity should be cabined by the new clinical studies that were essential to Sublocade's approval—and, in particular, by the fact that Indivior's studies did not consider stable patients. Said the Board: "We do not agree that certain features of the way the Sublocade studies were conducted impacts whether Sublocade's exclusivity blocks approval of Brixadi." FDA 427. In short, the FDA dismissed the difference between new OUD patients and clinically stable maintenance patients as a "simple change[] that make[s] little therapeutic difference." FDA 429.

In addition to discussing the scope of Sublocade's exclusivity, the Exclusivity Board

memorandum also considered whether Brixadi's approval might be blocked by the three-year exclusivity belonging to Probuphine. Reviewing the new clinical investigation that was essential to Probuphine's approval, the FDA concluded that the drug's safety and efficacy had only been established for the particular population of adult patients who had achieved clinical stability on 8 mg or less of sublingual buprenorphine. FDA 419. "Notably," the Board explained, "the indication for Probuphine specifically states that it is not appropriate for new entrants to treatment or for patients who have not achieved and sustained prolonged clinical stability at a low dose of buprenorphine (i.e., no more than 8 mg per day)." FDA 419-20. The FDA thus concluded that "the scope of approval was limited to such patients and therefore, the innovative change represented by Probuphine relates to the use of buprenorphine in [the specified] dosage form *for that indication*." FDA 419 (emphasis added). Brixadi was not blocked by this exclusivity, the FDA concluded, because Braeburn was "seeking approval for use in a different patient population," which was "not limited to" the terms of Probuphine's indication. FDA 420.

STANDARD OF REVIEW

"In a case involving review of a final agency action under the Administrative Procedure Act," the summary judgment standard set forth in Fed. R. Civ. P. 56(c) "does not apply"; rather, the court decid[es] whether as a matter of law the agency action is supported by the administrative record and is otherwise consistent with the APA standard of review." *Southeast Conference v. Vilsack*, 684 F. Supp. 2d 135, 142 (D.D.C. 2010). As relevant here, the APA requires a reviewing court to "hold unlawful and set aside agency action, findings, and conclusions found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law" or "in excess of statutory jurisdiction, authority, or limitations, or short of statutory right." 5 U.S.C. § 706(2)(A), (C). In general, these standards require an agency to

engage in reasoned decisionmaking: an agency must "examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (quotation marks omitted).

ARGUMENT

I. The FDA's determination of the scope of Sublocade's exclusivity contradicts the FDCA.

The FDA's exclusivity determination in this case is based on a fundamental misreading of the FDCA. The statute strictly limits the scope of new clinical trial exclusivity: a new drug is blocked only if it is "for the conditions of approval" of the drug with exclusivity. 21 U.S.C. § 355(c)(3)(E)(iii); *supra*, pp. 5-6; *see also* 21 C.F.R. § 314.108(b)(4). Put slightly differently, "[e]xclusivity under 21 U.S.C. § 355(c)(3)(E)(iii) is triggered by an overlap in the *conditions of approval* between the first-in-time 505(b) drug and the second-in-time 505(b)(2) NDA." *Veloxis*, 109 F. Supp. 3d at 117. Thus, a first-in-time drug cannot block the approval of a second-in-time drug for use under conditions for which the first-in-time drug is not approved.

But here, the FDA's exclusivity determination disregarded the statutory term "conditions of approval" and substituted the broader term "innovative change." According to the FDA, new clinical trial exclusivity extends to the full scope of the first drug's "innovative change," even if that change is broader—much broader—than the first drug's conditions of approval; the FDA will then refuse to approve *any* other drug that uses that innovation, even under conditions that the first drug does not reach. So, if the "conditions of approval" of the first-approved drug limit the use of the "innovative change" to certain conditions, the FDA's interpretation leaves patients who do not meet those conditions out of luck: no other formulation can come to market for them, *even if another sponsor conducts its own new clinical studies* and establishes the safety and

efficacy of the innovation for *broader* "conditions of approval" that would reach these new patients. Here, as the FDA recognized, "Sublocade's approved indication is limited to patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days." FDA 421. But the FDA gave Sublocade exclusivity that blocks *any* monthly depot injection of buprenorphine to treat moderate to severe OUD—even though Braeburn, not Sublocade, studied and established the safety of a depot injection without the seven-day induction period.

The FDA's substitution of "innovative change" for "conditions of approval" conflicts with the FDCA's plain language and is thus due no deference. *See, e.g.*, *Vill. of Barrington v. Surface Transp. Bd.*, 636 F.3d 650, 660 (D.C. Cir. 2011) (awarding agency no "special deference" when its decision "exceeded the statute's clear boundaries"). Moreover, even if the FDCA did not squarely foreclose the FDA's interpretation, that interpretation still would fail under step two of *Chevron* because it is unreasonable and impermissibly "frustrate[s] the policy that Congress sought to implement" by understanding new clinical trial exclusivity to bar some patients from *any* access to important medical innovations. *Shays v. FEC*, 528 F.3d 914, 919 (D.C. Cir. 2008) (quotation marks omitted).

A. The FDA's interpretation of the new clinical trial exclusivity provision is foreclosed by the plain text of the statute, which does not allow exclusivity to extend beyond a drug's "conditions of approval."

The FDCA limits the scope of a drug's exclusivity to its "conditions of approval." 21 U.S.C. § 355(c)(2)(E)(iii). As the statute makes clear, that phrase—"conditions of approval"—refers to the conditions under which the drug is approved for patient use, as stated on the drug's label. After all, the FDA can only "*approv[e]*" an NDA if it determines that the drug is "safe for use under the *conditions* prescribed, recommended, or suggested in the proposed labeling

thereof." 21 U.S.C. § 355(d) (emphases added); *see also Wyeth v. Levine*, 555 U.S. 555, 607 (2009). A "condition," in this context, is "a restricting or modifying factor." *Condition*, Merriam-Webster, https://www.merriam-webster.com/dictionary/condition (last visited May 13, 2019). And as the definite article "the" confirms, *all* of "the conditions of approval" count, not just "a condition" or some of them.

A drug's exclusivity therefore cannot be broader than the conditions for which it was approved. A drug is not approved for uses or under conditions that its labeling does *not* prescribe, recommend, or suggest. That means that if a drug's labeling restricts its approval to certain conditions, it restricts the drug's exclusivity as well. That reading accords perfectly with the structure and purpose of the exclusivity statute: the manufacturer of the first drug qualified for exclusivity by showing its drug to be safe and effective to treat certain patients and indications, and it receives exclusivity over the use of its innovation for those patients and indications. That scope is "commensurate with the degree of innovation required to earn [the] exclusivity," *Otsuka Pharm. Co. v. Price*, 869 F.3d 987, 993 (D.C. Cir. 2017), while leaving room for other companies to develop *new* innovations—products that can be used in *additional* patients under *additional* conditions and indications.

The FDA takes the contrary view that it should not read a manufacturer's "exclusivity more narrowly *than the scope of its innovation*." FDA 422 (emphasis added). But the "scope of its innovation" is not in the statute; "the conditions of approval" are. And the FDA's interpretation goes well beyond any permissible interpretation of the statutory phrase "conditions of approval"; it effectively reads the term "conditions" out of the exclusivity provision entirely, in violation of basic principles of statutory interpretation, and replaces it with an entirely new test of the FDA's own devising. That is impermissible. *E.g.*, *New York v. EPA*, 443 F.3d 880, 885

(D.C. Cir. 2006) ("[C]ourts must give effect to each word of a statute . . . .").

The facts of this case show just how remarkable the FDA's interpretation is. The FDA recognized in its exclusivity analysis that "Sublocade's approved indication is limited to patients who have initiated treatment with transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days." FDA 421. That limitation is clearly and expressly stated in the drug's labeling, including its INDICATIONS AND USAGE section.[4] And that limitation significantly limits patient access to the drug. *See supra*, p. 14; *see also* FDA 56 (one-quarter of patients who started taking oral buprenorphine in Sublocade's studies were never able to take Sublocade); FDA 220 (discussing need for depot product for emergency room patients). It is hard to imagine something that is more clearly made a "condition[] of approval" of Sublocade. Yet the FDA granted Sublocade exclusivity that failed to account for this limitation, but instead extended to *all* monthly depot buprenorphine products indicated for treatment of OUD. In other words, the scope of the exclusivity that the FDA granted to Sublocade is significantly broader than Sublocade's "conditions of approval."

That reasoning has no stopping point; it would apply equally if Sublocade could only be used after *thirty* days on oral buprenorphine, or *two hundred* days. It would even disregard

[4] The INDICATIONS AND USAGE section of a drug's labeling places important conditions on a drug's approval—so important, in fact, that "all indications listed . . . must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies" and any other uses "must not be implied or suggested" elsewhere in the labeling "if not included in this section." 21 C.F.R. § 201.57(c)(2)(iv). The INDICATIONS AND USAGE section must contain "[m]ajor limitations of use," *id.* § 201.57(a)(6), including any "specific conditions that should be met before the drug is used on a long term basis," *id.* § 201.57(c)(2)(i)(F). FDA guidance explicitly recognizes that limitations in the Indications and Usage section limit the scope of FDA approval: "The INDICATIONS AND USAGE section should clearly communicate the scope of the approved indication, *including the population to which the determination of safety and effectiveness is applicable*." FDA, *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products—Content and Format: Guidance for Industry—Draft Guidance*, at 3 (July 2018) (emphasis added).

differences in patient populations. For example, had Indivior been able to establish the safety and efficacy of its innovation in men, but not in women, the FDA's reasoning would apparently block approval of a competing buprenorphine product studied and found safe and effective for women—leaving women without access to the therapy in the name of exclusivity. Indeed, there is no reason why the FDA's reasoning would stop at treatment for opioid use disorder; if it had found the mere development of a monthly depot "innovative," it would have given Sublocade exclusivity over monthly depot buprenorphine *for any indication*, approved or unapproved. In any of those situations, the "innovation" would be the same, but the "conditions of approval" would be drastically different. This would have the perverse result of denying many patients access to the innovation *at all* during the exclusivity period, and in the case of a therapy like Brixadi, it potentially puts patients' lives at risk.

The FDA's misreading of the statute was fundamental to its exclusivity determination in this case. The FDA's exclusivity determination rested entirely on what the FDA determined to be Sublocade's "innovation," specifically the use of a "monthly depot product" to treat OUD. FDA 422. But the FDA completely ignored a vital limitation on Sublocade's "conditions of approval"—*i.e.*, the conditions under which the FDA approved the use of that monthly depot product. *See supra*, pp. 12-17, 21-22.

The FDA made little attempt to reconcile its decision with the statute's text. In a single, largely conclusory paragraph, the FDA inexplicably refused to limit the scope of Sublocade's exclusivity to the concededly limited scope of its "conditions of approval." FDA 421-422. Instead, as discussed above, the FDA focused on Sublocade's "innovation," reasoning that "[t]o determine that the scope of exclusivity encompassed [the seven-day dose-adjustment schedule] would interpret Sublocade's exclusivity more narrowly *than the scope of its innovation*." FDA

422 (emphasis added). But the statute does not give the FDA free rein to grant exclusivity to the full extent of whatever the FDA decides is the drug's "innovation." Rather, under the statute, the scope of a first-approved drug's exclusivity is limited by the scope of the drug's "conditions of approval"—*i.e.*, the circumstances in which the drug is indicated for use. Therefore, as a matter of the plain statutory text, a drug's exclusivity simply cannot extend to circumstances in which *the drug itself is not indicated for use*.

While the FDA acknowledged that Sublocade has only been approved for OUD patients who have initiated treatment and dose-adjusted on a take-home oral buprenorphine product for at least seven days, FDA 421, in some places the FDA tried to muddy the waters by asserting that Brixadi, like Sublocade, requires *some* oral buprenorphine. As an initial matter, however, the scope of Brixadi's conditions of approval does not alter the scope of Sublocade's exclusivity. And in any event, Brixadi requires only a single test dose administered in a doctor's office an hour before the first injection, rather than at least a week's worth of take-home oral buprenorphine—a clinically meaningful distinction. FDA 26, 220.

The FDA has recognized that this difference in the two drugs' "conditions of approval" has important implications. The limitation on the scope of Sublocade's approval, unlike that on Brixadi's, significantly limits access to the drug, as Sublocade cannot be used by patients who cannot complete the required oral-buprenorphine treatment, and cannot be used in contexts, like emergency rooms, in which there is an urgent need for immediate treatment with an injectable buprenorphine. FDA 56, 220. The limitation on Sublocade's approval also creates great risks to patients and their families, as the FDA has repeatedly recognized that oral-buprenorphine treatment carries with it significant risks to patient and public health, including buprenorphine misuse, diversion, and accidental pediatric exposure. *E.g.*, FDA 4, 7-8, 12, 108, 156, 158, 162,

164, 1220, 1223, 1229, 1231, 1279. Brixadi's test dose, by contrast, creates *none* of those risks, as the test dose can be administered at the same doctor's visit in which an injection is ultimately given, creating *no* need for take-home oral buprenorphine and ensuring certain and immediate treatment adherence. FDA 194. Because the FDA recognized the need for a depot injection that would not require any take-home buprenorphine, the FDA required that Indivior conduct postmarketing studies addressing whether it could be used *without* the seven-day initiation period. FDA 71; *see also supra*, p. 17. Of course, Braeburn has already done the very clinical studies that the FDA is requiring Indivior to conduct, and has developed a safe and effective drug that solves the precise problems Sublocade creates. But the FDA has concluded that Sublocade nevertheless *blocks* Brixadi from approval in the very situations in which the FDA has recognized that *Sublocade has not been approved as safe and effective*.

Given those differences, the FDA cannot save its interpretation with the unexplained suggestion that Brixadi's single test dose of oral buprenorphine, administered at the doctor's office, is equivalent to Sublocade's *one-week minimum* of take-home oral buprenorphine. Indeed, the FDA's clinical reviews repeatedly emphasize the important differences between the products. The FDA's clinical evaluation of Brixadi acknowledges that Brixadi *completely eliminates* the need for *any* take-home oral buprenorphine. *E.g.*, FDA 152 (Brixadi "would be the first extended-release [buprenorphine] product that can be administered to new entrants to [buprenorphine] treatment for this indication without an initial run-in on transmucosal medication"); FDA 157 (Brixadi "has the potential to provide several advantages, including . . . the ability to receive [buprenorphine] without take-home medications"); FDA 194 (explaining that Brixadi's clinical study "sought to demonstrate that their product would be appropriate for use *from the first patient visit* (following tolerability of a 4mg [buprenorphine] test dose), *so that*

no take-home use of sublingual buprenorphine would be necessary" (emphasis added)). Sublocade, by contrast, *requires* the use of take-home oral buprenorphine for at least a week (and perhaps longer)—a fact that, as the FDA repeatedly noted in its clinical review of Brixadi, was a significant issue for patient and public health. *E.g.*, FDA 158 (compared to existing treatment options, including Sublocade, Brixadi "[r]educes potential for diversion, misuse, abuse and accidental pediatric exposure").

In short, the plain statutory text requires that restrictions on the scope of a drug's *approval* lead to a corresponding restriction on the scope of the drug's *exclusivity*. The FDA has flouted that text, and has granted Sublocade an overbroad exclusivity that does not account for a key limitation on the "conditions of approval" for which the drug is indicated. For this reason alone, this Court should set aside the FDA's exclusivity determination.

B. The FDA's interpretation also fails at *Chevron* step two because it is unreasonable and subverts the intent of Congress.

Even if the FDA's interpretation were not plainly foreclosed by the FDCA, it would fail at *Chevron* step two because it is "unreasonable." *Loving v. IRS*, 742 F.3d 1013, 1022 (D.C. Cir. 2014). In particular, the FDA's approach to exclusivity in this case conflicts with Congress's desire to ensure that new clinical trial exclusivity does not stand in the way of new treatments for new patient populations not previously served by existing drugs.

As this Court has explained, new clinical trial exclusivity attempts to "strike a balance" between incentivizing rapid drug development while permitting immediate access to new treatments that are meaningfully distinct from existing ones. *See Veloxis*, 109 F. Supp. 3d at 107 (quotation marks omitted). Here, however, by allowing Sublocade to claim exclusivity that sweeps more broadly than the distinct patient populations for which it was approved, the FDA has disrupted the balance. It has not only blocked the approval of additional drugs for patients

already able to use Sublocade (as section 505(c)(3)(E)(iii) contemplates), but also blocked the approval of drugs for patients *who currently have no treatment option* because they are unable to use Sublocade (*e.g.*, patients who are unable to complete at least a week of initiation and dose adjustment on oral buprenorphine, or emergency-room patients). FDA 56, 220. Left unchecked, that logic would have profound implications for patients' access to new treatments, keeping new drugs off the market for substantial segments of the population without current treatment options.

To understand the problem more fully, imagine the FDA approves a new use of a known active ingredient to treat a certain condition, but that method has only been studied and proven safe and effective in, say, 2% of the patient population—patients who have the condition as a result of a rare genetic abnormality. The drug's label *expressly states* that it is indicated only for the rare patient with that genetic abnormality. The FDA would regard the "innovation" as the new use for the old drug, even though its "conditions of approval" are limited to that small fraction of the overall patient population. Now imagine another company conducts studies showing that the same "innovation" can also be effective in treating the other 98% of patients with that condition (who have the condition as a result of environmental factors rather than genetics). On the FDA's interpretation of the statute, as reflected in its exclusivity determination in this case, that new drug will be blocked by the prior drug's new clinical trial exclusivity because the new drug uses the same "innovation." That result not only ignores the statute's text, but it is also plainly unreasonable, as it puts patients' lives at risk, and grants a first-approved drug an exclusivity that extends far beyond the approved uses for that drug. The statute's text—and the FDA's past practice, *see infra* pp. 37-45—explicitly (and correctly) *reject* that outcome, yet the FDA's decision in this case inexplicably endorses it.

Not only does the decision below have the potential to significantly constrict patient

access to needed medications, but it also has the potential to do so indefinitely through the process of "evergreening." The sponsor of the drug with exclusivity can conduct new studies to gradually broaden its indications—and obtain a new period of exclusivity each time. In this way, the sponsor could use "three-year" new clinical trial exclusivity to indefinitely delay access to treatment for large segments of the patient population. Indeed, on the facts of this case, there is a possibility that if Sublocade's postmarketing studies lead, at some point in the future, to its approval for treatment of OUD patients *without* the need for a seven-day dose-adjustment period, it could receive an additional three-year exclusivity period for the new labeling and dosing instructions that blocks approval of Brixadi for *another* three years—even though Braeburn developed this innovation first.

Fortunately, nothing in the FDCA requires that result. The Act limits a drug product's new clinical trial exclusivity to its "conditions of approval." Because it ignored those conditions of approval here, the FDA's exclusivity determination for Sublocade was arbitrary, capricious, and contrary to law.

II. The FDA's determination concerning the scope of Sublocade's exclusivity is arbitrary and capricious.

The FDA exclusivity decision is not only in direct conflict with the statutory text, it is also arbitrary and capricious. The FDA violated two fundamental rules of reasoned decisionmaking by exhibiting clear internal inconsistency and by departing from longstanding agency precedent without explanation. For both of these reasons, the FDA's decision must be set aside. *See* 5 U.S.C. § 706(2)(A).

A. The FDA's exclusivity decision is internally inconsistent.

To survive arbitrary and capricious review, an agency's "reasoning cannot be internally inconsistent." *ANR Storage Co. v. FERC*, 904 F.3d 1020, 1024 (D.C. Cir. 2018); *see also*

Banner Health v. Price, 867 F.3d 1323, 1349 (D.C. Cir. 2017) (vacating as arbitrary and capricious an agency decision that "was internally inconsistent and inadequately explained" (quotation marks omitted)); *Dist. Hosp. Partners, L.P. v. Burwell*, 786 F.3d 46, 59 (D.C. Cir. 2015) ("We have often declined to affirm an agency decision if there are unexplained inconsistencies in the final rule."). The FDA's exclusivity decision fails that baseline requirement in multiple respects.

As discussed, the memorandum issued by the CDER Exclusivity Board addressed whether Braeburn's application for Brixadi was blocked by either Sublocade or Probuphine, both of which are buprenorphine products that are indicated for the treatment of opioid dependence. FDA 402. Reading the FDA's two sections, regarding the scope of exclusivity for these two products, is enough to induce whiplash; the agency's reasoning is completely irreconcilable.

Consider first the FDA's discussion of Probuphine. Probuphine was the first product to deliver buprenorphine using a subdermal implant, and it provides sustained treatment of opioid dependence over a six-month period. FDA 404-05, 419. In determining Probuphine's "conditions of approval," the FDA looked beyond the product's formulation and dosing interval to consider the patient population for which the product had received approval. Reviewing the relevant clinical trial, the FDA concluded that the drug's safety and efficacy had only been established for adult patients who had achieved clinical stability on 8 mg or less of sublingual buprenorphine. FDA 419. The FDA also relied on "the indication for Probuphine," which reflected those same patient-population restrictions. FDA 419-20. Based on these sources, the FDA concluded that "the scope of approval was limited to such patients and therefore, the innovative change represented by Probuphine relates to the use of buprenorphine in [the specified] dosage form *for that indication*." FDA 419 (emphasis added). In other words,

Probuphine's exclusivity would only block subdermal implant products that not only have a six-month dosing interval, but also are indicated "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." FDA 420. Brixadi was not blocked by this exclusivity, the FDA concluded, because Braeburn was "seeking approval for use in a different patient population," which was "not limited to" the terms of Probuphine's indication. *Id.*

The FDA's Probuphine decision is what the agency's exclusivity analysis is *supposed* to look like. By confining the scope of Probuphine's exclusivity to the limits on approval specified in its indication and supported by the relevant clinical studies, the FDA faithfully applied the statutory requirement that restricts a drug's exclusivity to its "conditions of approval." 21 U.S.C. § 355(c)(2)(E)(iii); *see supra* Part I. But when the FDA turned to evaluate Sublocade on the very next page of the exclusivity memorandum, the agency inexplicably changed course.

The FDA recognized that, as with Probuphine, Sublocade's clinical trials had studied the drug's safety and efficacy in only a limited patient population—here, patients who had "initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days." FDA 421. And the FDA acknowledged that, as with Probuphine, this limitation was built into "Sublocade's approved indication." *Id.*; *see also* FDA 97 (instructing health care providers to "[i]nitiate SUBLOCADE treatment *only* following induction and dose-adjustment with a transmucosal containing product" (emphasis added)); FDA 98 (instructing that patients "may *only* be transitioned to SUBLOCADE after a minimum of 7 days" of "treatment on transmucosal buprenorphine-containing product" (emphasis added)). Indeed, as discussed, *supra*, p. 13, the FDA required this narrowing of Sublocade's indication "to reflect the fact that"

participants in Indivior's key study "had to be dose-stabilized for at least seven days before initiating Sublocade." FDA 67. But whereas the FDA had concluded that the "conditions of approval" for Probuphine were limited by that drug's indication (FDA 419-20), the agency decided those same rules did not apply to Sublocade. Instead, the FDA concluded that "Sublocade's exclusivity is *not* constrained" by the treatment initiation and dose-adjustment schedule that its indication recognizes as a limit on approval. FDA 421-22 (emphasis added).

The FDA never even tried to reconcile this blatant inconsistency in its decision. In discussing Sublocade, the FDA simply asserted that the drug's "innovation" was broader than its approved indication, apparently on the theory that "buprenorphine had not been previously determined to be safe and effective for use in depot formulation that controlled release over a one month period." FDA 421, 422. But such reasoning could have just as easily been applied to Probuphine. After all, the FDA acknowledged that Probuphine "was the first buprenorphine product to deliver buprenorphine via a subdermal implant." FDA 419. Conspicuously, however, the FDA did *not* grant Probuphine three-year exclusivity to block all products that use its innovation by "deliver[ing] buprenorphine via a subdermal implant." Rather, the FDA quite properly concluded that "the conditions of approval" for the product—and thus the scope of its exclusivity—were narrowed by "the specific, limited indication" on Probuphine's labeling that restricted the drug's use to certain patients. FDA 406, 420. If the FDA had applied the same reasoning to Sublocade, it would have recognized that the drug's conditions of approval do not extend to all monthly depot formulations to treat OUD, but rather are confined to "the specific, limited" patient population identified in the product's indication and supported by its clinical studies. The FDA's failure to apply this logic to Sublocade is unexplained and unexplainable.

In fact, the FDA did not even apply consistent reasoning regarding a drug's "innovation"

when evaluating Sublocade itself. In discussing Sublocade's clinical studies, the FDA recognized that the studies "did not demonstrate that dosing intervals other than the monthly depot would be effective, or that the product was effective in treating subjects other than those with moderate to severe OUD." FDA 421. "[A]s a result," the FDA concluded, "Sublocade's exclusivity does not extend to dosing intervals other than monthly or to treatment of other patient populations." *Id.* But, of course, Sublocade's clinical studies *also* did not show that "the product was effective in treating subjects" that had not undergone seven days of treatment with take-home, oral buprenorphine. Yet the FDA disregarded that limitation on Sublocade's clinical studies and indication, granting Sublocade an exclusivity that barred approval of depot products that are clinically proven to be safe and effective in patient populations who were *not* part of Sublocade's clinical studies, and who thus fall outside the indication in Sublocade's label. FDA 421-22. Why the discrepancy? The FDA never says.

In short, because the FDA's exclusivity determinations were "internally inconsistent and inadequately explained," *General Chem. Corp. v. United States*, 817 F.2d 844, 846 (D.C. Cir. 1987) (per curiam), the Court should set aside the agency's conclusion that Sublocade's exclusivity extends beyond its indication to block approval of Brixadi as arbitrary and capricious.

B. The FDA's decision departs from agency precedent that prevents applicants from claiming exclusivity that goes beyond the limits of their clinical studies.

Agency action is also "arbitrary and capricious if it departs from agency precedent without explanation." *Ramaprakash v. FAA*, 346 F.3d 1121, 1124 (D.C. Cir. 2003); *see also FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009) ("[A]n agency may not . . . depart from a prior policy *sub silentio* or simply disregard rules that are still on the books."). Here, the FDA's exclusivity decision for Sublocade conflicts with agency precedent recognizing that exclusivity for submitting a new clinical investigation is limited to what the investigation

actually studied. But the FDA did not even *acknowledge* that its approach deviated from agency practice.

The statutory term "conditions of approval" has a well-established history of FDA interpretation. The FDA has consistently recognized that "[e]xclusivity does not extend beyond the *scope of the [drug's] approval* and does not cover aspects of the drug product *for which new clinical investigations were not essential*." FDA 415-16 (emphasis added); *accord* FDA 1391 (FDA exclusivity memorandum recognizing that three-year exclusivity is "*circumscribed* by the scope of the 'new clinical investigations' essential to the approval of the change" (emphasis added)). Thus, while the FDA has used the term "innovative change" to describe the differences between the drug with exclusivity and the drugs that came before it with the same active moiety, the FDA has *identified* that "innovative change" in each particular case by focusing on the patient populations at issue and the "underlying new clinical investigations that were essential to the [drug's] approval." FDA 415-16, 473.

In decisions applying this test, the FDA has established that a drug's exclusivity may not extend to block treatments for patient populations that were not studied in the applicant's new clinical investigations. The Astagraf XL matter is particularly on-point. *See supra*, p. 7. There, the FDA identified Astagraf XL's key innovation as the use of an extended release dosage form for tacrolimus, which allowed once-daily dosing. FDA 981. But the agency did *not* conclude that Astagraf XL could claim exclusivity for *any* tacrolimus product using that dosage form. Rather, the FDA explained that because "[t]he new clinical investigations essential to this innovation studied Astagraf XL for the prophylaxis of organ rejection in *de novo* kidney transplant patients," Astagraf XL's exclusivity only extended to that specific patient population. *Id.* Accordingly, the FDA determined that the drug's exclusivity did *not* block the approval of a

once-daily dosage form of tacrolimus indicated for "conversion patients." FDA 988-91. Notably, the FDA reached this conclusion even though Astagraf XL's indication extended to "prophylaxis of organ rejection in kidney transplant patients." FDA 988. The agency explained that despite the product's seemingly broad indication, its exclusivity was limited to *de novo* patients because the sponsor's new clinical investigations were restricted to such patients. FDA 990. In other words, the sponsor's exclusivity was "circumscribed by the scope of [its] new clinical investigations," which was tied to *de novo* patients, and could not "extend beyond this condition of approval." FDA 981.

The FDA's exclusivity decision here is clearly inconsistent with the Astagraf XL precedent because the agency extended Sublocade's exclusivity well beyond what Indivior actually studied in its new clinical investigations. The FDA arbitrarily disregarded at least two significant limitations in Indivior's pivotal efficacy study (RB-US-13-0001) that should have cabined Sublocade's conditions of approval under agency precedent.

1. Indivior's key clinical trial was limited to patients who initiated treatment with Suboxone sublingual film for three days, followed by a four- to eleven-day dose-adjustment period. FDA 407. The FDA recognized that this limitation created an "enriched" patient population for Sublocade's "essential" clinical trial because it excluded patients who could not navigate the extended dose-adjustment period with take-home oral buprenorphine. FDA 56. And as discussed, *supra*, p. 14, that number was substantial: "[o]ne-quarter of the patients who entered the run-in period" ultimately were not enrolled in the full study. FDA 56.

Indivior's clinical study thus provided no basis to conclude that Sublocade is safe and effective for patients who have not initiated with at least seven days of oral buprenorphine treatment. And there is good reason to believe that Sublocade may *not* be a viable option for that

patient population. The FDA has recognized that because Sublocade requires a 300 mg loading dose,[5] which is much higher than doses of oral buprenorphine typically used to initiate treatment, administering Sublocade without a significant run-up period of oral administration could precipitate "withdrawal, a clinically serious condition." FDA 71; *accord* FDA 6, 10-11, 65, 67. For that reason, the FDA required Indivior to conduct post-approval studies to evaluate whether Sublocade can be safety administered "without initial dose run-in on transmucosal buprenorphine." FDA 5, 10-11, 71.

Yet the FDA then disregarded the limited patient population Indivior studied by concluding that Sublocade's exclusivity extends to *all* depot products that deliver buprenorphine over a one-month period to treat moderate to severe OUD. FDA 427. Contrary to the FDA's cursory arguments (FDA 427, 431-32), this decision directly conflicts with the Astagraf XL precedent. The FDA simply asserted that the restriction in Indivior's clinical studies to an enriched patient population that could complete the "several day" titration should not limit the "conditions of approval for which Sublocade received exclusivity." FDA 432. According to the FDA, the difference between Sublocade and Brixadi "with regard to treatment initiation" was legally irrelevant because the products overlap in other ways: "Braeburn is still seeking approval of a monthly depot formulation that delivers an appropriate amount of buprenorphine to treat OUD." *Id.* But identical reasoning could have been applied in Astagraf XL. There too, the second application (for Envarsus XR) was seeking approval of a product whose indication would overlap with a previously approved product entitled to exclusivity—both products provided once-daily dosage forms of tacrolimus indicated for "prophylaxis of organ rejection in kidney

[5] In its exclusivity memorandum, the FDA stated that it "does not consider the 300 mg dose of Sublocade to be a 'loading' dose." FDA 430. That curious disavowal is completely inconsistent with the FDA's approval review for Sublocade, which repeatedly refers to Sublocade's 300mg initial dosage as a "loading dose." *See* FDA 5, 6, 11, 71.

transplant patients." FDA 988. The FDA nonetheless concluded that the first product could only block drugs indicated for treatment of "*de novo*" patients because that was the only population the applicant's clinical investigations had studied. FDA 988-91. *Ipse dixit* aside, the FDA provides no justification for the different result here.

Rather, the FDA's analysis consisted entirely of efforts to minimize the degree to which Brixadi improved on Sublocade's treatment regime and studied a patient population that Sublocade did not. FDA 427. The FDA did not explain how its assertions regarding Braeburn's product could possibly justify an over-broad exclusivity claim for Sublocade. Regardless, the FDA's reasoning that the "differences in details" between Sublocade's conditions of approval and Brixadi's proposed conditions were not "meaningfully different" (FDA 427, 429 n. 89, 432), is arbitrary and capricious in any event, because it contradicts the agency's own *repeated* statements acknowledging the significant benefits from a depot product like Brixadi that does not require take-home oral transmucosal buprenorphine for outpatient use, *see, e.g.*, FDA 4-5, 7-8, 12, 14, 157-58, 162, 164-65, 1220, 1222-23, 1229, 1231, 1279, 1396, 1442-23. Indeed, the benefits associated with reducing reliance on oral buprenorphine—and thus mitigating serious risks, including diversion and abuse—figured prominently in the FDA's decisions to approve the formulations for Sublocade and Probuphine. *See* FDA 4-5, 7-8, 1220, 1279, 1396, 1422-23. And as discussed, *supra*, p. 17, the FDA required Indivior to conduct a postmarketing study to determine whether Sublocade could be administered without seven days of oral buprenorphine titration precisely because the agency understood that "[i]n the current medical climate, there is great interest in initiating treatment using a depot formulation *as rapidly as possible*" in order to "reduc[e] the need to provide take-home" buprenorphine medication "for outpatient use," and that initiating depot treatment without oral buprenorphine titration "would contribute to safer use

of the drug." FDA 71 (emphasis added).

Based on the FDA's own reasoning, there is no question that Brixadi's proposed conditions of approval are "meaningfully different" than Sublocade's. FDA 432. As the FDA noted in its clinical review for Brixadi, the product "would be the first extended-release [buprenorphine] product that can be administered to new entrants to [buprenorphine OUD] treatment . . . without an initial run-in on transmucosal buprenorphine." FDA 152. Unlike Sublocade, Brixadi does not require an extended dose-adjustment period with oral buprenorphine, or *any* take-home administration; after a single test dose is administered at a doctor's office, patients can receive their first injection of Brixadi an hour later at the same appointment—meaning that "no take-home use of sublingual buprenorphine [is] necessary." FDA 194; *see also* FDA 220 (Brixadi clinical review) (recognizing potentially unique treatment options for Brixadi, resulting from its ability to "be administered after a single test dose of transmucosal buprenorphine); FDA 275, 277 (approved labeling for Brixadi, indicating approval to treat patients who have received "a single dose of transmucosal buprenorphine"). This ability to "initiat[e] . . . OUD treatment without a lead-in period" on take-home oral buprenorphine ensures patient compliance from day one and eliminates the risks of diversion and abuse. FDA 159; *see* FDA 157-58. The obvious importance of avoiding this lead-in period is vividly illustrated by the fact that a full quarter of the patients who enrolled in studies for Sublocade could not complete it and thus never received a Sublocade injection. FDA 56. The FDA's contention (FDA 427) that Brixadi's conditions of approval nonetheless "mirror" the conditions for Sublocade, merely because Brixadi requires a single in-office test dose of oral buprenorphine, is irreconcilable with the agency's findings about the significant clinical benefit from Brixadi's ability to avoid at least a week of titration on take-home oral buprenorphine. *See* FDA 71; *see*

also supra, pp. 17-18.[6]

2. The FDA also disregarded another important limit on Sublocade's clinical trials by discounting the exclusion of clinically stable patients from the studies' patient population. Sublocade's clinical trials did not show that the drug is safe and effective to treat patients who are clinically stable on take-home buprenorphine and are seeking to transition to a long-acting injectable product. *See* FDA 14 ("Indivior elected to study patients new to treatment . . . ."). And Sublocade is not approved for that use; to the contrary, the FDA required Indivior to conduct a postmarketing clinical study "to determine a process for transitioning patients with long-term stability on a transmucosal buprenorphine dose to a monthly dose of Sublocade without the use of a loading dose." FDA 5. As the FDA explained, "[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 would . . . contribute to safer use of the drug." FDA 71.[7]

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[6] The FDA stated that Braeburn did not establish that Brixadi "is safe and effective for use in treatment-naïve patients (i.e., patients who have not started treatment with an oral dose of buprenorphine)." FDA 427; *see also* FDA 429 n. 87. That statement appears to reference the fact that Brixadi requires a single test dose before administration—which Braeburn has never disputed. Once again, the FDA's apparent conclusion that the use of such a test dose collapses the difference between Brixadi and Sublocade is not only completely inconsistent with the agency's repeated findings that avoiding outpatient use of oral buprenorphine is a significant clinical benefit, but also ignores the significant clinical difference between a single test dose of buprenorphine versus initiating and dose-adjusting with oral buprenorphine. The FDA's observation that Brixadi involves a period of initial dosing titration also misses the point, because that titration does not occur under the same "conditions" as with Sublocade: with Brixadi, dose adjustment occurs during doctor's visits via injections. FDA 430. This process thus completely avoids all of the problems associated with take-home oral buprenorphine.

[7] As this statement by the FDA illustrates, clinical stability is distinct from dose stability. Clinical stability denotes prolonged use of buprenorphine therapy without significant relapse. The FDA approved Probuphine for patients who are "clinically stable on transmucosal buprenorphine." FDA 1444. The FDA further defined clinical stability in Probuphine's labeling as "sustained prolonged clinical stability on transmucosal buprenorphine" and on a "[s]table transmucosal buprenorphine dose . . . for three months or longer without any need for supplemental dosing or adjustments," and gave a list of additional factors to consider. FDA 1448. By contrast, dose stability references identification of the strength of buprenorphine

Under FDA precedent, the fact that Indivior did not study whether Sublocade is safe and effective for stable OUD patients should have restricted the scope of Sublocade's exclusivity. Once again, the situation closely mirrors the Astagraf XL matter, in which the FDA concluded that Astagraf could not claim exclusivity as to "conversion" patients who were seeking to switch immunosuppressive drugs because such patients were excluded from the sponsor's clinical investigations. *See* FDA 990. But the FDA brushed the limitation in Indivior's study aside, asserting that Sublocade's exclusivity extends to *all* monthly depot buprenorphine treatment for OUD, including clinically stable patients seeking to transition to a different maintenance therapy. In doing so, the FDA dismissed the difference between new OUD patients and clinically stable maintenance patients as a "simple change[] that make[s] little therapeutic difference." FDA 429.

The FDA's assertion that there is "little therapeutic difference" between new-to-treat and clinically stable groups is directly contradicted by the FDA's own statements shortly before and after its December 2018 determination of the scope of Sublocade's exclusivity—statements that the FDA has neither disavowed nor distinguished. In April 2018, in draft guidance to the industry to help it develop more depot buprenorphine products to treat OUD, the FDA described "new entrants to treatment" and patients "stable on other treatments" as clinically distinct groups requiring separate clinical studies. FDA 1804. The FDA repeated this recommendation in its final guidance issued in February 2019. *See* 2019 OUD Guidance, *supra*, at 5. Although Braeburn raised this discrepancy to the FDA (FDA 468), the agency never explained why, when evaluating Sublocade's exclusivity, it disregarded its own guidance for clinical trials.

Nor is there any basis in the record to support the FDA's apparent conclusion that

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therapy that achieves blocking effects and lessens withdrawal symptoms for an individual patient. FDA 6 ("The labeling will limit the use of Sublocade to patients who have been dose-stabilized on transmucosal buprenorphine for at least 7 days to mitigate the risk of precipitated withdrawal.").

Sublocade's conditions of approval extend to maintenance patients. Nothing in Sublocade's labeling states that it is approved, or appropriate for, patients who are clinically stable on other buprenorphine treatments.[8] And perhaps most telling, Sublocade's labeling contains no information about how to transition clinically stable patients onto Sublocade. By contrast, Probuphine, which is explicitly indicated for patients who are "clinically stable on transmucosal buprenorphine," FDA 1444, includes instructions that explain how healthcare providers can safely transition patients to Probuphine, FDA 1448. So too with the tentatively approved labeling for Brixadi. *See* FDA 226-27, 279.

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FDA precedent dictates that new clinical trial exclusivity is "circumscribed by the scope" of those clinical trials and the resulting limits on a drug's approval. FDA 981, 1391. And the FDA's exclusivity decision faithfully applied that rule as to one product, Probuphine. But then the FDA inexplicably departed from its precedent when addressing Sublocade, concluding that "Sublocade's exclusivity is *not* constrained" by the limits in the drug's indication or the gaps in its clinical investigations. FDA 421-22, 427-32 (emphasis added). The agency's selective and unacknowledged departure from its own precedent is arbitrary and capricious. *See Water Quality Ins. Syndicate v. United States*, 225 F. Supp. 3d 41, 79 (D.D.C. 2016).

CONCLUSION

The Court should grant Braeburn's motion for summary judgment.

[8] One part of Sublocade's labeling states that the healthcare provider should "[v]erify that patient is clinically stable on transmucosal buprenorphine before injecting SUBLOCADE (5.11)," FDA 95, but that statement is not discussing prolonged clinical stability. The statement cross-references section 5.11 of the labeling, which explains that it refers to dose stability. FDA 106.

Respectfully submitted,

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