NDA 210136

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Dear Mr. Derkacz:

This letter describes the Food and Drug Administration's (FDA's or the Agency's) determination, following reconsideration, regarding the effect of the 3-year exclusivity recognized for Sublocade (New Drug Application (NDA) 209819), on the approval of Brixadi (NDA 210136). Sublocade is a buprenorphine product in a monthly depot formulation developed for treatment of moderate-to-severe opioid use disorder (OUD). FDA approved the Sublocade NDA on November 30, 2017. The Brixadi NDA, which was submitted by Braeburn, Inc. (Braeburn) on July 19, 2017, proposed both a weekly and monthly formulation of Brixadi (Brixadi Weekly and Brixadi Monthly, respectively). Brixadi Monthly, like Sublocade, is a buprenorphine product in a monthly depot formulation for the treatment of moderate-to-severe OUD. On December 21, 2018, the Agency concluded that 3-year exclusivity recognized for Sublocade blocked final approval of Brixadi Monthly until November 30, 2020, but not Brixadi Weekly, and tentatively approved both formulations of Brixadi on that date.[1] The Agency provided a detailed explanation of its original exclusivity decision to Braeburn via letter dated February 28, 2019 (the February Decision Letter).[2]

The February Decision Letter described the framework applied by the Agency in analyzing the scope of 3-year exclusivity under the Federal Food, Drug, and Cosmetic Act (FD&C Act). In general, section 505(c)(3)(E)(iii) provides a period of limited exclusivity for certain approved drug products if new clinical investigations conducted by or on behalf of the applicant were essential to the application's approval. If a drug product is eligible for 3-year exclusivity, the statute provides that the Agency will not approve certain subsequent applications for the same "conditions of approval" as the exclusivity-protected product for a 3-year period. In its February Decision Letter, the Agency explained that, as reflected in decades of Agency practice, in

[1] Although the Agency informed Braeburn that 3-year exclusivity of Sublocade would not preclude approval of Brixadi Weekly, Braeburn has not submitted proposed labeling specific to Brixadi Weekly that would be required for its final approval.

[2] The analysis was also described in the Agency's internal exclusivity memorandum dated December 21, 2018.

interpreting section 505(c)(3)(E)(iii) it has consistently interpreted "conditions of approval" as the *innovation represented by the approved drug product* for which new clinical investigations were essential to approval.[3]

Applying this approach, FDA determined the "innovation" represented by Sublocade's approval—and thus its exclusivity-protected conditions of approval—is the effective delivery of buprenorphine in a depot formulation to treat moderate-to-severe OUD over a month-long period. In other words, a clinical study showing that the drug delivered an appropriate amount of buprenorphine over the monthly dosing period was essential to the approval of Sublocade and established the relevant "conditions of approval" under section 505(c)(3)(E)(iii). Because Brixadi Monthly also sought approval for the same conditions of approval, i.e., use as a monthly depot buprenorphine product for the treatment of moderate-to-severe OUD, FDA concluded that Sublocade's exclusivity barred approval of Brixadi Monthly.

On April 9, 2019, Braeburn filed suit in the U.S. District Court for the District of Columbia seeking review of the Agency's December 21, 2018 exclusivity decision, alleging that it was contrary to section 505(c)(3)(E)(iii) of the FD&C Act and arbitrary and capricious because it was inconsistent with some of FDA's other 3-year exclusivity decisions (Braeburn Litigation). On July 22, 2019, the court vacated the Agency's exclusivity decision and remanded to the Agency to reconsider Braeburn's NDA for Brixadi Monthly.[4] Specifically, the court held that FDA failed "to supply a standard by which a drug's innovation is defined. Without such a standard, the FDA has not reasonably interpreted the statute and the [February Decision Letter] must be vacated."[5] The court further held that without such a standard "the agency's determination of whether the Brixadi Monthly was subject to a right of exclusivity belonging to Sublocade was arbitrary and capricious."[6]

Consistent with the court's opinion, FDA has reconsidered its analysis of 3-year exclusivity and the scope of Sublocade's innovation pursuant to section 505(c)(3)(E)(iii) of the FD&C Act. The Agency's reconsideration has drawn on the expertise of medical and scientific experts within FDA's Center for Drug Evaluation and Research (CDER), including the Division of Anesthesia, Analgesia, and Addiction Products (Division or DAAAP), and has involved substantial consultation among Agency components including CDER's Office of New Drugs (OND), Office of Generic Drugs (OGD), and Office of Regulatory Policy (ORP), as well as other relevant Agency components.

The Agency's conclusion on reconsideration results in the same outcome described in the February Decision Letter: that 3-year exclusivity recognized for Sublocade precludes final approval of Brixadi Monthly until November 30, 2020. This result follows from the Agency's interpretation of section 505(c)(3)(E)(iii) of the FD&C Act, as explained below. On remand, the

[3] February Decision Letter, at 14.

[4] *Braeburn Inc. v. FDA*, 389 F. Supp. 3d 1 (D.D.C.).

[5] Id. at 27.

[6] Id. at 30.

Agency continues to interpret the statute such that the "conditions of approval" protected by 3-year exclusivity are the innovation for which new clinical investigations were essential to approval. However, this letter more clearly articulates the Agency's application of that standard.

The court held that the phrase "conditions of approval" is ambiguous.[7] To interpret "conditions of approval" for the purpose of determining the scope of a product's exclusivity, FDA first asks what unique clinical question the new clinical investigations essential to approval answer for the first time about the safety and/or efficacy of the active moiety for the relevant use. The Agency makes this determination by evaluating the product at issue in comparison to previously approved drugs with the same active moiety and determining for which aspects of the drug product the clinical investigations were essential to approval. In many cases, the Agency also must consider whether the scope of the innovation is further defined by particular characteristics of the drug product, supported by the new clinical investigations essential to its approval, such that it would not bar approval of a subsequent product that does not share these same characteristics. As explained below, the Agency makes this assessment by considering whether, in FDA's expert judgment, these characteristics would be clinically meaningful with respect to use of the drug product.[8]

Applying this framework, the Agency upon reconsideration concludes that the innovation supported by Sublocade's new clinical investigations essential to approval is the effective delivery of buprenorphine in a depot formulation to treat moderate-to-severe OUD over a month-long period in patients who have initiated prior treatment with a buprenorphine product. Sublocade is labeled for use in patients who had initiated[9] treatment with a transmucosal buprenorphine-containing product, followed by dose-adjustment[10] for a minimum of 7 days.[11] The initiation and dose-adjustment period address the potentially serious risk of precipitated withdrawal, which can occur in opioid-dependent patients when starting treatment with a buprenorphine product.

Precipitated withdrawal is a known risk associated with buprenorphine treatment. Like Sublocade, proposed labeling for Brixadi Monthly requires prior initiation with a different buprenorphine product to address the risk of precipitated withdrawal, although—consistent with

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[7] Id. at 22.

[8] The Agency describes how it determines whether a characteristic is "clinically meaningful" for purposes of evaluating the scope of 3-year exclusivity below. We note that although this term is also used in other regulatory contexts, its use here is specific to the 3-year exclusivity context, where we must balance the competing statutory goals of innovation and competition in determining the scope of exclusivity supported by new clinical investigations essential to approval.

[9] "Initiation" in this context generally refers to administration of a first dose of buprenorphine product in patients who are actively ill.

[10] "Dose-adjustment" generally describes the process of administering progressively greater (or lower) doses until a target dose or appropriate therapeutic dose is achieved. The term "titration" is similar to dose-adjustment (typically a dose would be titrated to increasing levels, while dose-adjustment could include lowering the dose).

[11] Sublocade Labeling, Oct. 2019, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209819s009lbl.pdf.

differences in how Sublocade and Brixadi Monthly were studied—the details of the two products' initiation protocols are not the same.[12] The Agency does not consider those differences in how the two products address the risk of precipitated withdrawal upon initiating treatment for OUD (before transitioning to the monthly products at issue here) to be clinically meaningful to the use of the monthly products themselves in a way that would take Brixadi Monthly outside the scope of Sublocade's exclusivity-protected conditions of approval because in both cases, introduction of the monthly product occurs only after initiation and dose adjustment with another buprenorphine product. The sponsors of both Sublocade and Brixadi Monthly addressed the risk of precipitated withdrawal in different ways in their clinical investigations essential to approval. The clinically meaningful characteristic of Sublocade for exclusivity purposes is not how the applicant addressed the issue of precipitated withdrawal in its development program, but that it did so with new clinical investigations supporting approval of the monthly depot formulation.

Because Brixadi Monthly is proposed for the same condition of approval (the effective delivery of buprenorphine in a depot formulation to treat moderate-to-severe OUD over a month-long period in patients who have initiated prior treatment with a buprenorphine product), it remains blocked by Sublocade's exclusivity. The result gives effect to the text, context, and purpose of the 3-year exclusivity statute in that it defines and preserves an incentive for the innovation that, in the Agency's judgment, was represented by Sublocade's approval. As before, the Agency concludes that exclusivity applicable to Sublocade would not preclude approval of *Brixadi Weekly*; if Braeburn were to decide to market that product independently, it could do so following submission and approval of appropriate labeling. This result is also consistent with FDA's previous exclusivity decisions, as discussed below.

I. FACTUAL BACKGROUND

This section describes the background relevant to the Agency's reconsidered exclusivity determination. Section I.A describes the history of buprenorphine products developed for treatment of OUD, generally, and sections I.B through I.D provide detailed background regarding Sublocade, Brixadi, and Probuphine[13], including information about the new clinical investigations that were essential to their approval. The remainder of the section summarizes the exclusivity analysis set forth in the February Decision Letter and the Braeburn Litigation.

A. History of Buprenorphine Drug Products

Buprenorphine, a partial agonist at the mu-opiate receptor, was developed as a treatment for

[12] Proposed labeling for Brixadi—which would address both Brixadi Weekly and Brixadi Monthly—recommends a one-week titration period beginning with a 4-mg test dose of transmucosal buprenorphine (as a screen for precipitated withdrawal), followed by specified doses of Brixadi Weekly. The proposed labeling explains that initiating treatment with Brixadi Monthly in new entrants to treatment has not been studied.

[13] As explained below, Probuphine is a 6-month subdermal implant buprenorphine product that was approved prior to Sublocade. The February Decision Letter considered whether 3-year exclusivity recognized for Probuphine would bar approval of Brixadi. The 3-year exclusivity period applicable to Probuphine has since expired. While the Probuphine approval preceded submission of the Sublocade and Brixadi applications, this background section addresses Sublocade and Brixadi first because those products are necessarily the focus of the decision on remand.

opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone, a full agonist at the mu-receptor.[14] Opioid use disorder is a chronic, relapsing disease characterized by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and physical consequences.[15] In 2015, two million adults were identified as having OUD,[16] reflecting the growing health concern of the opioid crisis and the national rise of cases of opioid abuse and misuse.

Like methadone, buprenorphine's activity at the mu-receptor was expected to relieve patients' urge to use illicit opioids. Also, like methadone, buprenorphine's long duration of action was expected to allow patients to achieve a steady state with daily dosing, without the alternating highs and lows associated with opioid abuse that impair daily functioning. At sufficiently high doses, buprenorphine blocks full opioid agonists from achieving their full effects, deterring abuse of these substances for buprenorphine-maintained patients. However, compared to methadone, buprenorphine is less likely to cause life-threatening respiratory depression and was therefore expected to be more suitable for take-home use.

Due to its partial agonist properties, the euphorigenic effects of buprenorphine are understood to reach a "ceiling" at moderate doses, beyond which increasing doses of the drug do not produce the increased effect that would result from full opioid agonists like methadone. This was expected to limit its attractiveness as a drug of abuse, an additional feature permitting take-home use.

In addition, when a partial agonist displaces a full agonist at the receptor, the relative reduction in receptor activation can produce withdrawal effects. Individuals dependent on full agonists may therefore experience sudden and severe symptoms of withdrawal (i.e., precipitated withdrawal) if they start to use buprenorphine. Precipitated withdrawal presents a potentially serious risk in patients beginning treatment with buprenorphine, with symptoms that can include excessive vomiting, diarrhea, intense sweating, and dehydration. Products to treat opioid addiction might address withdrawal risks through use of specified steps, including initiation and dose-adjustment periods, prior to beginning therapeutic treatment.

The first buprenorphine product approved for the treatment of opioid dependence was Indivior Pharmaceuticals, Inc.'s (Indivior's) Subutex (NDA 020732), which was approved in 2002.[17]

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[14] NDA 209819 Cross-Discipline Team Leader Review and Summary Basis for Approval (CDTL Review), Nov. 30, 2017, at 13.

[15] See *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V)*. The phrase "opioid use disorder" is generally used to refer to the condition previously referred to as "opioid dependence."

[16] 2015 National Survey on Drug Use and Health (SAMHSA); Monthly Morbidity Weekly Report (MMWR), 2016; 65(50-51);1445–1452 [Center for Disease Control (CDC)].

[17] Subutex is no longer marketed, as reflected by its listing in the Discontinued Drug Product List in FDA's "Approved Drug Products With Therapeutic Equivalence Evaluations" (generally known as the "Orange Book"), available at https://www.accessdata.fda.gov/scripts/cder/ob/). The Orange Book also reflects that FDA made a finding that the product was not discontinued for reasons of safety or efficacy. The ownership of the NDAs for several buprenorphine products has changed since first approval. For ease of reading, we have referred only to the current NDA ownership.

Buprenorphine products have also been approved for treatment of pain.[18]

B. Sublocade

Indivior's Sublocade was approved on November 30, 2017. It is labeled for the treatment of moderate-to-severe OUD in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.[19] Sublocade is formulated as a subcutaneous injection for delivery of buprenorphine in the abdominal area once monthly.[20]

Sublocade's labeling states in section 2.2, "Initiating treatment with SUBLOCADE as the first buprenorphine product has not been studied. Initiate SUBLOCADE treatment only following induction and dose-adjustment with a transmucosal buprenorphine-containing product." It further states in section 2.4, "Patients appropriate for SUBLOCADE are adults who have initiated treatment on a transmucosal buprenorphine-containing product…."

Sublocade is a drug-device combination product with 18% buprenorphine base in the ATRIGEL Delivery System in a prefilled syringe.[21] The ATRIGEL Delivery System is a non-aqueous solution consisting of a biodegradable polymer, 50:50 poly (DL-lactide-co-glycolide) with a carboxylic acid end group (PLGH) dissolved in a water-miscible, biocompatible solvent, N-methyl-2-pyrrolidone (NMP). Following injection, NMP diffuses out of the polymer matrix and the polymer precipitates, trapping buprenorphine inside and forming an amorphous solid depot in situ. Then, over a 1-month period, the depot releases buprenorphine by diffusion as the polymer degrades.

The Sublocade NDA relied on published literature to support the safety assessment of the excipients which form the ATRIGEL delivery system. The Sublocade application also cross-referenced another Indivior application for buprenorphine (Subutex, NDA 020732) and included the results of a product-specific clinical program. The Division identified the following studies

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[18] Products approved for treatment of pain include Indivior's Buprenex (NDA 018401), a parenteral formulation of buprenorphine for intramuscular and IV use, which was approved in 1981; Purdue Pharma's Butrans (NDA 021306), a transdermal extended-release formulation approved in 2010; and Biodelivery Science International's Belbuca (NDA 207932), a buccal film approved in 2015. There are also FDA-approved drug products that contain buprenorphine HCl and naloxone HCl in a fixed combination, e.g., Suboxone (NDA 022410), which are not relevant for purposes of this exclusivity analysis. As explained further in section II, when determining if a pending application may be blocked by unexpired exclusivity, among other things, FDA considers whether the pending application is seeking approval of a drug with the same active moiety or combination of active moieties as the NDA with unexpired exclusivity.

[19] Sublocade Labeling, Oct. 2019, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209819s009lbl.pdf.

[20] It is approved in two dosage strengths, 300 mg (in a 1.5 mL vol.) (the initiation dose) and 100 mg (in a 0.5 mL vol.) (the monthly maintenance dose), in a prefilled syringe with a 19 G 5/8-inch needle.

[21] NDA 209819 CDTL Review, Nov. 30, 2017, at 12.

as new clinical investigations essential to approval of the NDA:[22]

- **Blockade Study (RB-US-13-0002)**: Study RB-US-13-0002 was a phase 2, inpatient behavioral pharmacology study to determine the doses for the pivotal study and identify the dose regimen required to block exogenous opioids using hydromorphone challenge tests. In this study, patients were started, and doses were titrated, on Suboxone sublingual film (buprenorphine/naloxone; NDA 022410). Patients were then exposed to challenges with placebo and two hydromorphone doses, in random order (a method used for assessing drug liking).[23] The subjects received monthly Sublocade injections. The study was primarily intended to demonstrate that, following 300 mg subcutaneous injection of the drug product, "Drug Liking" scores measured after challenge with 6 mg or 18 mg of hydromorphone intramuscular injections were not higher than those measured after challenge with a placebo injection.[24]

- **Pivotal Efficacy Study (RB-US-13-0001)**: Study RB-US-13-0001 was a phase 3, randomized, placebo-controlled, parallel group multi-center study to assess the efficacy, safety and tolerability of multiple subcutaneous injections of two Sublocade dosing regimens over 6 months (24 weeks) in treatment-seeking subjects with moderate-to-severe OUD: Dosing Regimen 1: 300 mg x 6 doses (once monthly); Dosing Regimen 2: 300 mg for the first 2 months, followed by maintenance dosage of 100 mg for the next 4 months (all once monthly). Study RB-US-13-0001 had a 2 week, open-label run-in, including initiation of treatment with Suboxone sublingual film for 3 days and a 4- to 11-day dose-adjustment period with Suboxone sublingual film to achieve doses ranging from 8 to 24 mg/day.[25] Subjects who completed the open-label, run-in phase and met the criteria were randomized and included in a double-blind treatment phase. To be eligible for randomization, subjects should have had no significant opioid craving or withdrawal after at least 7 days of Suboxone sublingual therapy. The primary efficacy endpoint was the cumulative distribution function of the percentage weeks of abstinence measured by weekly Urine Drug Screen negative for opioids and self-reports negative for illicit opioid use from week 5 through 24. A key secondary endpoint was treatment success, where a responder was defined as any subject with $\geq$ 80% of urine samples negative for opioids combined with self- reports negative for illicit opioid use between week 5 and week 24.

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[22] NDA 209819 Exclusivity Summary, November 30, 2017. The Exclusivity Summary also listed Safety Study RB-US-13-0003, which was an open-label, long-term safety and tolerability study of monthly depot buprenorphine in treatment-seeking subjects with OUD. However, that study rolled over patients from Study RB-US-13-0001 and was intended to establish general safety. The study did not permit broader use of the drug, nor did it establish safety of buprenorphine for a new patient population. See 54 FR 28899 (noting that general safety studies, which neither permit broader use of a drug nor establish safety of a drug for a new patient population, should not qualify for exclusivity). Thus, we have concluded that the Safety Study was not a new clinical investigation essential to approval.

[23] In the drug challenge sessions, subjects were administered different doses of hydromorphone (0 mg, 6 mg, and 18 mg) in varying order to assess "drug liking".

[24] NDA 209819 CDTL Review, at 33.

[25] A dose-adjustment period was used to avoid precipitated withdrawal in subjects in which a high starting dose of buprenorphine might otherwise lead to displacement of a full opioid agonist.

> This efficacy study, together with pharmacodynamic data, showed that Sublocade blocks the effects of exogenously administered opioids for the entire inter-dose period. Both dosing regimens were found to be effective.

Regarding the clinical studies required for approval, the Sublocade CDTL Review[26] stated the following:

> Although buprenorphine products have been approved for the treatment of opioid dependence, there have been no monthly depot formulations previously approved. To ensure that the amount of buprenorphine provided, and the proposed dosing interval were suitable to support the proposed indication, the Applicant was required to support a finding of efficacy for this product with two adequate and well-controlled clinical trials or one adequate and well-controlled clinical trial and a human behavioral pharmacology study demonstrating the ability of the product to block the effects of exogenous opioids (blockade study).

Sublocade was thus the first once-monthly depot buprenorphine product to be approved for the treatment of moderate-to-severe OUD in patients who have initiated prior treatment with a buprenorphine product.

C. Brixadi

On July 19, 2017, Braeburn submitted NDA 210136 for Brixadi Weekly and Brixadi Monthly formulations, which received a complete response letter on January 19, 2018, citing significant manufacturing issues as well as concerns about the clinical datasets. Braeburn resubmitted NDA 210136 on June 26, 2018, and both Brixadi formulations were tentatively approved on December 21, 2018. The INDICATIONS AND USAGE section of the proposed labeling tentatively approved for combined Brixadi Weekly and Brixadi Monthly states:

> BRIXADI is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. BRIXADI should be used as part of a complete treatment plan to include counseling and psychosocial support.

The proposed labeling further includes separate dosing and administration instructions for the *weekly* formulation (which is suitable for patients who have initiated treatment with a single dose of transmucosal buprenorphine) and for the *monthly* formulation (which is *not* suitable for patients who have only initiated treatment with a single dose of transmucosal buprenorphine but would be suitable for patients who were already using the weekly formulation or were already being treated with another buprenorphine product). Section 2.3 (Recommended Dosing) explains that patients new to buprenorphine treatment begin treatment after administration of a

[26] NDA 209819 CDTL Review, at 12.

test dose, followed by administration of doses of Brixadi Weekly based on a specified titration schedule.[27] Transition from Brixadi Weekly to Brixadi Monthly is based on clinical judgment.

Section 2.4 (Patient Selection) of Brixadi's proposed labeling also provides the following information:

> Patients appropriate for BRIXADI (weekly) are:
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> 1. adults who have tolerated a single 4 mg dose of a transmucosal buprenorphine-containing product. The test dose of transmucosal buprenorphine-containing product should be administered based on instructions in the appropriate product label.
> 2. adults who are currently being treated with a transmucosal buprenorphine-containing product.
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> Patients appropriate for BRIXADI (monthly) are adults who are currently being treated with a transmucosal buprenorphine-containing product. BRIXADI (monthly) is not intended for patients who are new to buprenorphine treatment.

The labeling for Brixadi also states that, to avoid precipitating opioid withdrawal syndrome, practitioners should administer a test dose of transmucosal buprenorphine before initiating treatment with Brixadi Weekly. The labeling explains that patients already being treated with a transmucosal buprenorphine-containing product can be switched to Brixadi Weekly or Brixadi Monthly.

NDA 210136 is a 505(b)(2) NDA that relies on the Agency's findings of safety and efficacy for Subutex (NDA 20732), sublingual buprenorphine tablets, as well as data from Braeburn's own clinical development program.

Brixadi is a drug-device combination product containing a modified-release formulation of

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[27] In particular, it states the following: The recommended weekly dose in patients not currently receiving buprenorphine treatment is 24 mg of BRIXADI (weekly) titrated up over the first week of treatment as follows:

> (1) To avoid precipitating an opioid withdrawal syndrome, administer a test dose of transmucosal buprenorphine 4 mg when objective signs of mild to moderate withdrawal appear.
>
> (2) If the dose of transmucosal buprenorphine is tolerated without precipitated withdrawal, administer the first dose of BRIXADI (weekly), 16 mg.
>
> (3) Administer an additional dose of 8 mg BRIXADI (weekly) within 3 days of the first dose to achieve the recommended 24 mg BRIXADI (weekly) dose.

If needed, during this first week of treatment, administer an additional 8 mg dose of BRIXADI (weekly), waiting at least 24 hours after the previous injection, for a total weekly dose of 32 mg BRIXADI (weekly).

Administer subsequent BRIXADI (weekly) injections based on the total weekly dose that was established during Week One. Dosage adjustments can be made at weekly appointments with the maximum BRIXADI (weekly) dose being 32 mg.

buprenorphine in a ready-for-use prefilled syringe designed for administration by subcutaneous injection.[28] The modified release formulation is based on the Fluid Crystal (FC) delivery technology that results in a liquid-to-gel Phase transition that occurs when the lipid-based FC system is exposed to the subcutaneous tissue. The Phase transition from liquid to gel proceeds from the periphery of the FC injectable towards the center of the product by absorption of minute quantities of water. Thus, the injection of Brixadi Weekly or Brixadi Monthly depot into subcutaneous tissue results in an immediate and spontaneous formation of a matrix providing release of the drug over the designated period in vivo.

The Brixadi Weekly and Brixadi Monthly formulations differ in dosage strengths and excipients. Brixadi Weekly is proposed for doses of 8, 16, 24, and 32 mg, while Brixadi Monthly is proposed for doses of 64, 96, and 128 mg.[29]

To support approval of the NDA, the applicant submitted the following clinical studies demonstrating safety and efficacy of the product:[30]

- **Blockade Study (HS-13-478)**: Study HS-13-478 was an inpatient behavioral pharmacology study intended to establish the ability of CAM2038 (the development name for Brixadi) 24 mg weekly and CAM2038 32 mg weekly to completely block the effects of an exogenous opioid.

- **Pivotal Efficacy Study (HS-11-421)**: Study HS-11-421 was a randomized, double-blind, double-dummy, active-controlled, parallel group, non-inferiority study of 6-months duration in patients with moderate-to-severe OUD who met the criteria for "new entry" to treatment (not receiving buprenorphine treatment within at least 60 days of study screening) treated with CAM2038 in two phases: Phase 1 (CAM2038 weekly for 12 weeks individually titrated beginning with dose of 8 mg weekly), followed by Phase 2 (CAM2038 monthly at various doses versus treatment with sublingual buprenorphine comparator (Subutex)).

- **Safety Study (HS-13-499)**: Study HS-13-478 was an open-label, Phase 3, multisite study to evaluate the long-term safety of the product in both weekly and monthly formulations.

D. Probuphine

The Agency approved Probuphine (NDA 204442) on May 26, 2016 as a 6-month subdermal implant for the maintenance treatment of opioid dependence in patients who have achieved and

[28] FDA Briefing Document, Joint Meeting of Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, Nov. 1, 2017.

[29] The Brixadi Weekly formulation contains buprenorphine, soybean phosphatidylcholine, glycerol dioleate, and ethanol. Brixadi Monthly contains buprenorphine, soybean phosphatidylcholine, glycerol dioleate, and N-methyl-2-pyrrolidone.

[30] NDA 210136, Clinical Review, Jan. 12, 2018, at 37.

sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (i.e., doses of no more than 8 mg/day of Subutex or Suboxone sublingual tablet or generic equivalent).[31] The active ingredient is buprenorphine hydrochloride, for which buprenorphine is the active moiety. NDA 204442 for Probuphine was originally submitted by Titan Pharmaceuticals, Inc. (Titan) on October 31, 2012. The NDA received a Complete Response letter on April 30, 2013.[32] The NDA was resubmitted on August 27, 2015.

Probuphine is a subdermal implantable formulation of buprenorphine HCl in a solid matrix of ethylene vinyl acetate polymer shaped into implants or rods. Each implant contains 74.2 mg of buprenorphine (equivalent to 80 mg of buprenorphine HCl). The matrix formulation of the implants is intended to provide a steady-state delivery of buprenorphine that maintains a stable plasma level of the drug for six months.[33] The recommended dose is four implants every six months.

The Probuphine NDA was submitted as a 505(b)(2) application and relies, in part, on FDA's findings of safety and effectiveness for Subutex (buprenorphine) sublingual tablets (NDA 020732) and Suboxone (buprenorphine and naloxone) sublingual tablets (NDA 020733). The original NDA included, among other things, two phase 3 safety and efficacy trials, two safety extension trials, and two clinical pharmacology studies.[34] Data initially submitted for Probuphine did not support a broader indication initially sought by the applicant, specifically, for patients newly-entering treatment for opioid dependence. However, this data suggested that a distinct subpopulation—of clinically stable patients—could benefit from Probuphine, and that more limited patient population was then studied in a subsequent trial.[35]

The NDA resubmission included a clinical efficacy trial to support the use of the product in clinically stable patients with opioid dependence, maintained on 8 mg/day or less of a buprenorphine-containing transmucosal product.[36] Upon the sponsor's amendment of the proposed indication for the NDA to state that the product is intended as maintenance treatment for opioid-dependent patients who have been clinically stable for a sustained period of time on low to moderate doses of transmucosal buprenorphine, the Agency approved the NDA. The Division determined that only the clinical study submitted with the Probuphine resubmission, which provided data in this patient population, was a new clinical investigation essential to

[31] Probuphine prescribing information, approved on May 25, 2016, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204442Orig1s000lbl.pdf; NDA 204442, Cross-Discipline Team Leader Review (CDTL Review) at 1 (Feb. 13, 2016).

[32] NDA 204442, Clinical Review at 12 (Feb. 8, 2016).

[33] NDA 204442, Clinical Review at 13.

[34] NDA 204442, Clinical Review at 25.

[35] Id. at 6-7.

[36] Id.

approval of the NDA:[37]

- **Efficacy Study (PRO-814):** Study PRO-814 was entitled "A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine Subdermal Implants." In addition to the attributes noted in the title of the study, it also included a non-inferiority design, and three phases: A Screening Phase (Weeks -2 to -1), a 24-week Maintenance Phase, and a 2-week Follow-Up Phase. The stated primary objective of the study was to demonstrate maintenance of treatment efficacy when transferring adult outpatients with opioid dependence that were clinically stabilized on 8 mg or less of sublingual buprenorphine to four Probuphine implants (administered at once) compared to treatment as usual with sublingual buprenorphine. This study was of a 6-month duration.

Probuphine was thus approved 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 (i.e., doses of no more than 8 mg/day of Subutex or Suboxone sublingual tablet or generic equivalent). Approved labeling explains that Probuphine implants are inserted subdermally in the upper arm for 6 months of treatment and are removed by the end of the sixth month. The labeling specifies that Probuphine is not appropriate for new entrants to treatment and patients who have not achieved and sustained prolonged clinical stability, while being maintained on buprenorphine 8 mg per day or less of a Subutex or Suboxone sublingual tablet or generic equivalent.

E. February Decision Letter

In the February Decision Letter, the Agency considered whether final approvability of Brixadi was affected by 3-year exclusivity recognized for either of two previously approved products: Probuphine and Sublocade. As described in the February Decision Letter, the Agency made this assessment by applying a framework based on FDA's interpretation of section 505(c)(3)(E)(iii) of the FD&C Act. Briefly, under section 505(c)(3)(E)(iii) a drug product may be eligible for a period of 3-year exclusivity if new clinical investigations (excluding bioavailability studies) conducted by or on behalf of the product's applicant are essential to the product's approval. The Agency has consistently interpreted "conditions of approval" in section 505(c)(3)(E)(iii) as the *innovation represented by the approved drug product* for which new clinical investigations are essential to approval. That is, where the Agency determines that a drug product is eligible for 3-year exclusivity, it has considered the scope of that exclusivity to be defined by the innovation represented by the new clinical investigations essential to its approval when compared to previously approved products with the same active moiety. A subsequent product with the same condition(s) of approval (i.e., the same innovation(s)) as the exclusivity-eligible product would be barred from approval during the exclusivity period regardless of whether it differed in other

[37] NDA 204442 Exclusivity Summary, May 24, 2016. Note that four other studies were also listed in the Exclusivity Summary as essential to approval, PRO-805, PRO-806, PRO-807, and PRO-811, but were later determined not to be essential to approval.

ways from the exclusivity-eligible product. Where multiple drug products with the same active moiety are approved sequentially, the exclusivity of each subsequent drug product is typically narrower in scope relative to exclusivity recognized for the previously approved product(s).

Applying this interpretation, the Agency first considered whether Probuphine barred approval of Brixadi. It noted that "buprenorphine had been approved in several previous NDAs, including in some cases for treatment of opioid dependence[,]" but that Probuphine was the first buprenorphine product to deliver buprenorphine via a subdermal implant.[38] Further, it explained that "the dose approved for Probuphine was a level likely to be effective for the treatment of opioid dependence only for a limited population of certain stable patients, so the scope of approval was limited to such patients and therefore, the innovation represented by Probuphine relates to the use of buprenorphine in that dosage form for that indication."[39] The Agency noted that Probuphine's indication specifically states that it is not appropriate for new entrants to treatment or those who have not achieved and sustained prolonged clinical stability at a low dose of buprenorphine (i.e., no more than 8 mg per day). Based on this, the Agency concluded that the conditions of approval for which the clinical investigation was essential are the effectiveness of a single-entity buprenorphine subdermal implant product for a 6-month period, for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product.[40] Because neither Brixadi Monthly nor Brixadi Weekly share these conditions of approval, the Agency determined that the scope of exclusivity for Probuphine did not bar final approval of either Brixadi formulation.

The Agency then addressed the 3-year exclusivity recognized for Sublocade. The analysis considered the previous buprenorphine approvals, including approval of Probuphine, and assessed the new clinical investigations essential to Sublocade's approval in relation to those earlier approvals. The February Decision Letter explained that:

> Sublocade was the first buprenorphine product to be available as a subcutaneous injection intended to provide the controlled release of buprenorphine over a one-month period. In light of the previous buprenorphine approvals, including Probuphine, we consider Sublocade's approval for use of a monthly buprenorphine depot for the treatment of OUD to represent an innovative change for which the new clinical trials conducted by Indivior were essential to approval. This is because buprenorphine had not been previously determined to be safe and effective for use in depot formulation that controlled release over a one-month period, and information from new clinical investigations was necessary to establish the safety and efficacy of buprenorphine for that use, and to establish that Sublocade delivered buprenorphine at a plasma level suitable for treating new entrants to treatment for OUD (after an initial oral dose).[41]

[38] February Decision Letter, at 18.

[39] Id.

[40] Id.

[41] Id. at 19.

In connection with the analysis described in the February Decision Letter, the Agency considered arguments raised in submissions on behalf of Braeburn, including in a July 23, 2018 letter submitted by counsel for Braeburn.[42] Braeburn's letter argued that Brixadi should not be blocked by Sublocade because, in light of previous buprenorphine approvals, the innovation represented by Sublocade did not extend beyond use of its specific formulation. It also argued that, even if Sublocade's innovation was understood to extend more broadly, various characteristics of Brixadi should cause it to fall outside the scope of Sublocade's exclusivity. In particular, the company argued that Sublocade's exclusivity should only block products that have the same indication, "run in"/dose adjustment phase, instructions for transitioning patients from transmucosal products, injection sites (limited to rotating abdominal sites), and patient population (limited to OUD patients only).[43] FDA disagreed, concluding that "[t]he finding from the Sublocade studies that buprenorphine can be delivered in an appropriate amount to treat OUD by a monthly depot product is not necessarily limited to or dependent on the particular treatment initiation, dose adjustment schedule, or strengths."[44]

F. Braeburn Litigation

On April 9, 2019, Braeburn filed suit in the U.S. District Court for the District of Columbia seeking review of the Agency's December 21, 2018 exclusivity decision, alleging that it was contrary to section 505(c)(3)(E)(iii) of the FD&C Act and arbitrary and capricious because it was inconsistent with some of FDA's other 3-year exclusivity decisions. The court issued its decision on July 22, 2019, vacating the Agency's exclusivity decision and remanding to FDA "to reconsider, with deliberate speed, Braeburn's application for final approval of Brixadi Monthly."[45]

As a threshold matter, the court held that the phrase "conditions of approval" in the three-year exclusivity provision of the FD&C Act "refers in some way to the protected drug product's characteristics, [but] how to determine the subset of characteristics that matters for purposes of exclusivity is ambiguous."[46] The court also held that FDA's approach of "identifying 'the conditions of approval' as the features of the drug that the clinical investigations essential to approval showed, for the first time, to be safe and effective—in other words, a drug's innovative features—respects the relationship between [505(c)(3)(E)(iii)]'s complementary clauses [and] Congress's intent, and is a first step toward filling the statutory ambiguity."[47] It concluded,

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[42] See Letter from Scott M. Lassman to Grail Sipes, Director of the Office of Regulatory Policy, CDER (July 23, 2018 letter).

[43] February Decision Letter, at 25.

[44] February Decision Letter, at 20.

[45] *Braeburn Inc. v. FDA*, 389 F. Supp. 3d 1, at 32.

[46] Id. at 23.

[47] Id. at 24.

though, that the Agency's exclusivity decision "lacks a standard by which innovation is determined."[48] The court concluded that the Agency failed to explain what principle it applied in determining the scope of a product's innovation.[49] That is, "[r]ather than identifying a principle that guides how to conceive the limits of a drug product's innovation, the agency instead, at least here, defined innovation in the broadest possible sense."[50]

The court recognized that the determination of whether characteristics of one product are meaningfully different from that of another for purposes of the exclusivity analysis involves a degree of scientific judgment.[51] However, "before the stage at which the FDA determines that differences between two drug products are not 'meaningful' for purposes of exclusivity, the FDA must explain the standard, consistent with [505(c)(3)(E)(iii)], that informs how the innovation against which those differences are judged is defined."[52]

The court also determined that the Agency's conclusion regarding the scope of Sublocade's exclusivity appeared inconsistent with two other exclusivity decisions. The first involved FDA's consideration of the scope of Probuphine's exclusivity as described in the February Decision Letter. The court observed that, in that instance, the Agency "limited the drug's defined innovation, in part, based on the patient population participating in the essential clinical investigation."[53] In contrast, while Sublocade was approved only for patients who have undergone a specified initiation and dose adjustment, "Sublocade's innovation was not defined as limited by the patient group on which the drug was tested."[54] The court also addressed FDA's exclusivity decision regarding Astagraf XL (tacrolimus ER capsules), a product approved in 2013 for prophylaxis of organ rejection in patients receiving a kidney transplant.[55] The Agency concluded that the scope of Astagraf's exclusivity was limited to its use in a specific population

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[48] Id. at 24 ("If exclusivity under § [505(c)(3)(E)(iii)] protects innovation, the FDA needs a rationale, based in the statute, to define the boundaries of a drug product's innovation. On that front, the agency advances no principle—legal or scientific that guides its determination. Without any intelligible decisional principle for identifying innovation, the FDA's standard simply supplants the ambiguous phrase 'the conditions of approval' for the ambiguous term 'innovation.'").

[49] Id. at 25 ("The FDA's statements…leave the most important question unanswered: what *standard*—legal or scientific—has the FDA applied to define Sublocade's innovation in the broad manner set forth in the Letter Decision? Why is dosing interval a way in which Sublocade's innovation is limited, but the drug product's high-loading dose of 300 mg, the patient population on which it was tested, or other details of its specific treatment regime, are not?").

[50] Id.

[51] Id. at 26.

[52] Id. at 26. The court noted that, "[i]n the end, the attributes that Braeburn believes take Brixadi Monthly outside the scope of Sublocade's innovation might not, in fact, do so…. [But], to analyze properly whether Brixadi Monthly is 'for the conditions of approval' of Sublocade, the FDA must first explain what separates the elements of the essential clinical investigations incorporated into that definition of a drug product's innovation from those that are irrelevant, and why the identified dividing line reasonably applies § [505(c)(3)(E)(iii)]." Id. at 27.

[53] Id. at 28.

[54] Id. at 29.

[55] Astagraf Labeling, Indications and Usage section.

(*de novo* patients) because its new clinical investigations studied only that group; as a result it did not block approval of a subsequent tacrolimus product—Envarsus ER—in a distinct patient population. The court concluded that the Agency's February Decision Letter "does not answer why the FDA could define Astagraf XL's innovation as limited to *de novo* patients without improperly depriving its sponsor of the benefit of the underlying innovation but the same could not be done for Sublocade."[56]

II. STATUTORY AND REGULATORY BACKGROUND

This section describes the legal background relevant to 3-year exclusivity under the FD&C Act. Section II.A provides general background on drug approval pathways. Section II.B explains the Agency's framework for applying 3-year exclusivity and its statutory basis. This discussion addresses the concerns raised by the court in the Braeburn Litigation and provides additional description of the framework previously discussed regarding the principles FDA uses in determining the scope of 3-year exclusivity recognized for an eligible drug product.

A. Drug Approval Pathways Under the FD&C Act

Section 505 of the FD&C Act establishes approval pathways for three categories of drug applications: (1) 505(b)(1) NDAs, (2) 505(b)(2) NDAs, and (3) 505(j) abbreviated new drug applications (ANDAs).

1. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FD&C Act requires that an application contain, among other things, "full reports of investigations" to show that the drug for which the applicant is seeking approval is safe and effective.[57] NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as *505(b)(1) NDAs* or *stand-alone NDAs*.

FDA will approve a 505(b)(1) NDA if it finds that the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling, and that it meets other applicable requirements.[58]

2. 505(b)(2) NDAs and ANDAs: Abbreviated Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman

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[56] *Braeburn Inc. v. FDA*, 389 F. Supp. 3d 1, at 29.

[57] See section 505(b)(1)(A) of the FD&C Act. A 505(b)(1) NDA must also include: a full list of the articles used as components of the proposed drug product; a full statement of the composition of such drug; a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; samples of the drug as necessary; proposed labeling for the drug; and pediatric assessments. Id.

[58] See, e.g., section 505(b)(1), 505(c) and 505(d) of the FD&C Act and 21 CFR part 314.

Amendments)[59] amended the FD&C Act to add section 505(b)(2) and 505(j) as well as other conforming amendments. These provisions describe abbreviated pathways for 505(b)(2) NDAs and ANDAs, respectively.[60] The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions.[61] These pathways permit sponsors to rely on what is already known about the previously approved drug, which both allows for a speedier market entry than would be possible with a full, stand-alone 505(b)(1) NDA and leads to increased competition.[62]

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c) of the FD&C Act. A 505(b)(2) NDA must meet both the "full reports" requirement in section 505(b)(1)(A) and the same safety and effectiveness standard as a stand-alone NDA. Unlike a stand-alone NDA though, in a 505(b)(2) NDA, some or all of the safety and/or effectiveness information relied upon for approval comes from investigations not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.[63] Thus, the difference between a 505(b)(2) NDA and a stand-alone NDA is the source of the information relied on for approval. Whereas a stand-alone NDA is supported entirely by studies that the sponsor owns or to which it has a right of reference, the 505(b)(2) applicant may also rely on, for example, the Agency's findings of safety and/or effectiveness for one or more previously approved drugs.[64]

A 505(b)(2) application can be submitted for a change to a previously approved drug and, in

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[59] Public Law 98-417 (1984).

[60] Section 505(j) of the FD&C Act generally requires that an applicant for an ANDA demonstrate that its product is bioequivalent to the listed drug it references (RLD) and is the same as the RLD with respect to active ingredient(s), dosage form, route of administration, strength, previously approved conditions of use, and, with certain exceptions, labeling. As the pending matter involves only 505(b)(2) NDAs, it is not necessary to discuss the ANDA pathway here.

[61] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[62] See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Meyers Squibb Co. and E.R. Squibb & Sons, Inc. v. Royce Labs., Inc.*, 69 F.3d 1130, 1132-34 (Fed. Cir. 1995).

[63] Section 505(b)(2) of the FD&C Act provides for approval of an application:

> for a drug for which the [safety and efficacy investigations] . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . . .

See 21 CFR 314.3(b) (defining *right of reference or use*).

[64] See Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Katherine M. Sanzo, Esq., Lawrence S. Ganslaw, Esq., Morgan, Lewis & Bockius LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq., Gillian R. Woollett, Ph.D., Vice President Regulatory Affairs, Biotechnology Industry Organization; William R. Rakoczy, Esq., Lord, Bissell & Brook LLP (Oct. 14, 2003) (originally assigned Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 and changed to Docket Nos. FDA-2001-P-0369, FDA-2002-P-0390,

some instances, may describe a drug product with substantial differences from a listed drug.[65] When a 505(b)(2) applicant seeks to rely on a finding of safety and effectiveness for a previously approved drug product, the applicant must establish that its basis for relying on a previous approval is scientifically justified. A 505(b)(2) applicant can *bridge*[66] its proposed product to the previously approved product by submitting, for example, studies that measure the relative bioavailability (BA)[67] of the two products, or other appropriate scientific information.

FDA has described its interpretation of section 505(b)(2) of the FD&C Act in a series of public statements and proceedings beginning in 1987, including the 1989-1994 Hatch-Waxman rulemaking process, the 505(b)(2) Draft Guidance, and previous citizen petition responses.[68] FDA's interpretation of section 505(b)(2) is intended to permit a sponsor to rely to the greatest extent possible under the law on what is already known about a drug. The 505(b)(2) pathway permits sponsors and the Agency to target drug development resources to studies needed to support the proposed difference or innovation from the listed drug on which the 505(b)(2) application seeks to rely.[69]

B. 3-Year Exclusivity Under the FD&C Act

This section explains the framework applied by the Agency in determining whether 3-year exclusivity recognized for an approved drug product blocks approval of a subsequent pending 505(b)(2) application. It explains the Agency's reasoning in interpreting "conditions of approval" as the innovation established by the new clinical investigations essential to approval of the eligible product. As further discussed below, to identify this innovation, the Agency asks: what unique clinical question(s) about the safety and/or efficacy of the active moiety for the

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and FDA-2003-P-0274, respectively, as a result of FDA's transition to Regulations.gov) (505(b)(2) Citizen Petition Response).

[65] In October 1999, the Agency issued a draft guidance for industry entitled "Applications Covered by Section 505(b)(2)" (505(b)(2) Draft Guidance) which states that "[a] 505(b)(2) application may be submitted for an NCE [new chemical entity] when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference." 505(b)(2) Draft Guidance at 3, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[66] The "bridge" in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug, or between the proposed product and a product described in published literature, to justify reliance scientifically on certain existing information for approval of the 505(b)(2) NDA.

[67] Bioavailability data provide an estimate of the amount of the drug absorbed, as well as provide information related to the pharmacokinetics (PK) of the drug. See, e.g., FDA's Draft Guidance for Industry: "Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations" (March 2014) (BA/BE NDA/IND Draft Guidance), at 3.

[68] See, e.g., 505(b)(2) Citizen Petition Response and Letter from Steven K. Galson, M.D., M.P.H., Director, CDER, FDA, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP; Stephan E. Lawton, Esq., Biotechnology Industry Organization; Stephen G. Juelsgaard, Esq., Genentech (May 30, 2006) (originally assigned Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355 and changed to Docket Nos. FDA-2004-P-0339, FDA-2003-P-0003, FDA-2004-P-0214, and FDA-2004-N-0059, respectively, as a result of FDA's transition to Regulations.gov) (2006 Citizen Petition Response).

[69] 21 CFR 314.54(a) states that a 505(b)(2) application "need contain only that information needed to support the modification(s) of the listed drug."

relevant use do the new clinical investigations essential to approval answer for the first time?

In sum, as explained below, the conditions of approval to which 3-year exclusivity applies is defined by its innovation supported by the new clinical investigations, which the Agency identifies by comparing the product to previously approved drugs. The scope of innovation thus is determined relative to previous drug approvals. Its scope may be further defined by particular characteristics of the product supported by the new clinical investigations essential to approval, if these characteristics are clinically meaningful.

1. General Framework

An application for a drug containing a previously approved active moiety (including a 505(b)(2) application) is generally eligible for 3 years of exclusivity if the statutory and regulatory standards are satisfied. The statute and regulations for 3-year exclusivity describe which approved NDAs and supplements are eligible for 3-year exclusivity and which are barred or blocked from approval by that exclusivity.

For NDAs, section 505(c)(3)(E)(iii) of the FD&C Act states:

> *If an application submitted under subsection (b) [of this section] for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) [of this section], is approved after [September 24, 1984,] and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant*, the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) [of this section] if the investigations described in clause (A) of subsection (b)(1) [of this section] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.[70]

The first clause (italicized) in section 505(c)(3)(E)(iii) of the FD&C Act, often referred to as the eligibility clause, describes the applications eligible for 3-year exclusivity. FDA has interpreted the term "active ingredient" in the phrase "active ingredient (including any ester or salt of the active ingredient)" to mean active moiety.[71] Under the eligibility clause in section 505(c)(3)(E)(iii), applications for drugs that are not eligible for 5-year NCE exclusivity (because they contain an active moiety "that has been approved in another application")[72] are eligible for

[70] See Section 505(c)(3)(E)(iii) of the FD&C Act (emphasis added); see also 21 CFR 314.108(b)(4)(iv).

[71] See 21 CFR 314.3(b) (definition of active moiety).

[72] The longest period of exclusivity provided under the Hatch-Waxman Amendments is 5-year NCE exclusivity. See section 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act. A 5-year exclusivity period is provided for a

3-year exclusivity if they include new clinical investigations (other than bioavailability studies), essential to approval of the application, that were conducted or sponsored by or on behalf of the applicant. FDA's implementing regulations interpret certain aspects of the statutory language regarding 3-year exclusivity. Among other things, they define the terms *clinical investigation,*[73] *new clinical investigation*,[74] *essential to approval*,[75] and *conducted or sponsored by the applicant.*[76]

The second clause in section 505(c)(3)(E)(iii) of the FD&C Act (underlined), often referred to as the bar clause, describes the conditions under which certain 505(b)(2) NDAs will be barred or blocked from approval by the 3-year exclusivity and thus describes the scope of 3-year exclusivity.

Under the Agency's interpretation of the bar clause, a determination of the scope of 3-year exclusivity under section 505(c)(3)(E)(iii) involves two steps. The first step of the scope inquiry focuses on the drug with 3-year exclusivity. The phrase "such drug in the approved subsection (b) application" in the bar clause refers to the earlier use of the term "drug" in the eligibility clause, i.e., "a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application," that is, the drug which includes a previously approved active moiety. Thus, 3-year exclusivity for a drug only bars drugs that contain the same active moiety (or the same active moieties for fixed-combination drugs).

The second step of the scope inquiry focuses on the scope of the new clinical investigations essential to approval conducted or sponsored by the applicant. Under this aspect of the inquiry, the scope of the new clinical investigations essential to approval conducted or sponsored by the

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drug "no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under [section 505(b)]." FDA has interpreted this exclusivity to generally prevent an applicant from submitting a 505(b)(2) NDA or ANDA for a drug that contains the active moiety approved in the protected drug for a 5-year period from the date of approval of the protected drug. Five-year NCE exclusivity does not block submission or review of stand-alone 505(b)(1) NDAs.

[73] "Clinical investigation" is defined as "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects." 21 CFR 314.108(a).

[74] "New clinical investigation" is defined, in relevant part, as "an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product." 21 CFR 314.108(a).

[75] "Essential to approval" means "with regard to an investigation, that there are no other data available that could support approval of the NDA." 21 CFR 314.108(a).

[76] "Conducted or sponsored by the applicant" is defined, in relevant part, as "that before or during the investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor of the investigational new drug application under which the investigation was conducted, or the applicant or the applicant's predecessor in interest, provided substantial support for the investigation." 21 CFR 314.108(a). The preamble to FDA's final rule on Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338 (Oct. 3, 1994) also described examples of studies that would not qualify for exclusivity. For example, FDA explained that: "[c]hanges that would not warrant exclusivity are, as discussed in the preamble to the proposed rule, changes in labeling that involve warnings or other similar risk information that must be included in the labeling of generic competitors." 59 Fed. Reg. 50,357.

applicant determines the "conditions of approval" for which certain subsequent applications are barred.

The Agency's interpretation of "conditions of approval," and its approach to assessing whether exclusivity blocks approval of a 505(b)(2) application, are discussed below.

2. Interpretation of "Conditions of Approval"

Although neither the statute nor the regulations define the phrase *conditions of approval* for purposes of determining whether exclusivity blocks approval of a 505(b)(2) application,[77] the preamble to FDA's proposed rule governing exclusivity (1989 Proposed Rule)[78] addresses the Agency's interpretation. It makes clear FDA's view that conditions of approval for the purposes of 3-year exclusivity means the innovative change for which new clinical investigations are essential to approval:

> Exclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product. Thus, if the innovation relates to a new active moiety or ingredient, then exclusivity protects the pioneer drug product from other competition from products containing that moiety or ingredient. If the innovation is a new dosage form or route of administration, then exclusivity protects only that aspect of the drug product, but not the active ingredients. If the innovation is a new use, then exclusivity protects only that labeling claim and not the active ingredients, dosage form, or route of administration.[79]

FDA interprets the scope of exclusivity to be related both to the underlying *new clinical investigations* that were essential to the approval and to aspects of the approval that were supported by those new clinical investigations. Exclusivity does not cover aspects of the drug product for which new clinical investigations were not essential.

Thus, in the case of an application submitted for a drug that contains a single active moiety that has been previously approved (a non-NCE), if the application contains reports of new clinical investigations (other than bioavailability studies) essential to approval of the application that were conducted or sponsored by or for the applicant, section 505(c)(3)(E)(iii) bars FDA from approving a 505(b)(2) NDA for such drug (i.e., another single-entity drug containing that active moiety) for the exclusivity-protected conditions of approval for a period of 3 years. This exclusivity, however, does not bar FDA from approving a 505(b)(2) NDA for a drug containing a different active moiety. Neither does it block a 505(b)(2) NDA that does not otherwise seek approval for the exclusivity-protected conditions of approval.

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[77] 21 CFR 314.108(a) and 314.108(b)(4)(iv).

[78] See generally Abbreviated New Drug Application Regulations, 54 FR 28872 (July 10, 1989).

[79] 1989 Proposed Rule at 28896-97.

The Agency's interpretation ties the incentive provided by 3-year exclusivity to the innovative change supported by the new clinical investigations conducted by an applicant, reflecting the way in which the statute's *eligibility clause* and *bar clause* operate together. That is, it considers the "conditions of approval" to which exclusivity applies under the bar clause to be determined by the "new clinical investigations (other than bioavailability studies) essential to the approval of the application"[80] that establish the drug product's eligibility for exclusivity. In this way, "[t]he [FD&C Act] sets up a 'logical relationship between the change in the product for which the new clinical investigations were essential to approval of the [NDA], and the scope of any resulting three-year exclusivity.'"[81] The interpretation "respects the relationship between [section 505(c)(3)(E)(iii)]'s complementary clauses, Congress's intent, and is a first step toward filling the statutory ambiguity."[82] The legislative history indicates that Congress intended 3-year exclusivity to protect only innovations that required the support of new clinical investigations essential to approval.[83]

Moreover, we believe that other interpretations of "conditions of approval" would lead to results that are inconsistent with the statute's purpose. For example, under a different interpretation, *conditions of approval* might be understood to mean all of the conditions stated in FDA-approved labeling. That is, the conditions of approval might include *all* the information in approved labeling, meaning that exclusivity for one product would block a subsequent product's approval only where the labeling is exactly the same. But this interpretation would risk rendering an eligible product's exclusivity meaningless because of the high likelihood that a subsequent product's labeling would differ from the protected product's labeling in at least some ways. If any difference in labeling were sufficient to take a subsequent product outside of the scope of a prior approved product's exclusivity, 505(b)(2) applications (which are not subject to a "same labeling" requirement) would almost never be blocked.[84] Interpreted in this manner, section 505(c)(3)(E)(iii), which governs the application of 3-year exclusivity to 505(b)(2) applications, might be considered superfluous because the only products that might be blocked by such narrow exclusivity likely would be ANDAs, which are subject to the exclusivity provision in section 505(j)(5)(F)(iii) of the FD&C Act. It is also significant that section 505(c)(3)(E)(iii) does not make reference to approved labeling. Thus, it is reasonable to conclude that the scope of exclusivity is not limited to blocking products only with the same labeling. At the same time, if "conditions of approval" means that any overlap in the approved uses or characteristics of the product with exclusivity might block approval of a subsequent 505(b)(2) application with the same active moiety, then almost any 505(b)(2) application with the same active moiety would be blocked. Courts have upheld FDA's view of the relationship between *new clinical investigations* that were essential to the approval and the scope of 3-year

[80] FD&C Act § 505(c)(3)(E)(iii).

[81] *See Veloxis*, 109 F. Supp. 3d at 120-21.

[82] *Braeburn Inc. v. FDA*, 389 F. Supp. 3d 1, at 24.

[83] *See* 59 Fed. Reg. 50338, at 50357 (Oct. 3, 1994).

[84] As the court noted in its decision in the Braeburn Litigation discussed above, "[p]rotecting exclusivity rights only if a follow-on product matches every condition listed in the first product's label would curtail exclusivity narrowly to exclude only precisely identical drug products, a result plainly at odds with Congress's goal of incentivizing research with market exclusivity." *Braeburn Inc. v. FDA*, 389 F. Supp. 3d 1, at 21.

exclusivity.[85] Given that 505(c)(3)(E)(iii) is silent on reliance, a subsequent 505(b)(2) application need not rely upon the drug product with unexpired exclusivity to be considered within the scope of and blocked by that product's exclusivity.[86]

3. Defining the Scope of Exclusivity

The link between the scope of exclusivity and the new clinical investigations essential to approval means that, in assessing the scope of 3-year exclusivity for a drug product containing the same active moiety or same active moieties as a previously approved drug product, the Agency looks at the innovation represented by the later-approved drug product relative to the previously approved drug product.[87]

In identifying the innovation, the Agency asks a key question: for what aspects relative to previously approved drug products were the new clinical investigations essential to approval? More specifically, we ask *what unique clinical question(s) about the safety and/or efficacy of the active moiety for the relevant use do the new clinical investigations essential to approval answer for the first time?* By framing the inquiry in this way, the Agency seeks to ensure that the incentive provided by exclusivity rewards sponsors for conducting studies that will answer clinical questions relevant to the drug's approval, and not for establishing or confirming what is already known about the drug.

To determine the clinical questions for which the new clinical investigations were essential to approval, the Agency evaluates what has been shown in clinical investigations for the product at issue in comparison to what was known about previously approved drug products with the same active moiety. The analysis is, by definition, context-specific: a change that may have significance as an innovation in one instance—that is, a change for which studies were needed to demonstrate its safety or efficacy—may not require further studies in another instance, for example, in another therapeutic area. And, the nature of what aspect(s) of a drug will constitute an innovation must be determined on a case-by-case basis.[88]

i. Effect of Previously Approved Drug Products on Scope of 3-Year

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[85] *Veloxis Pharms, Inc. v. U.S. Food & Drug Admin.*, 109 F. Supp. 3d 104, at 115-24 (D.D.C. 2015); *Zeneca Inc. v. Shalala*, No. CIV.A. WMN-99-307, 1999 WL 728104, at *12 (D. Md. Aug. 11, 1999) *aff'd*, 213 F.3d 161 (4th Cir. 2000) ("The exclusivity extends only to the 'change approved in the supplement'"); *AstraZeneca Pharm. LP v. Food & Drug Admin.*, 872 F. Supp. 2d 60, 79 (D.D.C. 2012) *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013) ("[T]he Court concludes that 21 U.S.C. § 355(j)(5)(F)(iv) is ambiguous. The FDA has reasonably interpreted and applied the applicable statute . . ."). Although the latter two cases involved the statutory provision for ANDAs, rather than the provision at issue here (i.e., section 505(c)(3)(E)(iii)), the provision pertaining to ANDAs interpreted by the courts includes the same language regarding the scope of 3-year exclusivity. The courts upheld as reasonable FDA's interpretation of the relationship between the scope of clinical studies that earned exclusivity, the change in the product that resulted, and the scope of the exclusivity earned.

[86] *Veloxis Pharms, Inc. v. U.S. Food & Drug Admin.*, 109 F.Supp.3d 104, at 116-120.

[87] A product eligible for 3-year exclusivity under section 505(c)(3)(E)(iii) will by definition not be the first approved product containing the active moiety (or active moieties) at issue.

[88] For example, this may be the case because of new technologies or evolving understanding of a disease area.

Exclusivity

Because the Agency evaluates the scope of a drug product's innovation in relation to previously approved drug products, the scope of 3-year exclusivity for a drug product is generally affected by a previously approved drug product containing the same active moiety or the same active moieties.

In practice, where two drug products that have the same active moiety or same active moieties are sequentially approved, the result is often that the scope of exclusivity of the second drug product is limited – often narrower in scope – relative to any exclusivity recognized for the first drug product. This is because exclusivity is recognized only for new clinical investigations that are "essential to approval," which "means, with regard to an investigation, that there are no other data available that could support approval of the NDA."[89] As explained above, exclusivity does not protect aspects of the drug product for which new clinical investigations were not essential – that is, it does not cover aspects of the product which have already been demonstrated to be safe and effective (or which could be supported without the new clinical investigations).

If an earlier-approved drug product was approved for a particular condition of approval, new clinical investigations would not be considered "essential" to support the same condition of approval for a later-approved drug product containing the same active moiety. Rather, the new clinical investigations would be considered essential only to support conditions of approval for the later-approved drug product that are different from the conditions of approval of the earlier-approved drug product. Thus, because 3-year exclusivity generally covers only the differences from a previously approved product, as a practical matter each later-approved product typically will have a narrower scope of exclusivity than the product(s) approved previously.

Under FDA's interpretation, the scope of 3-year exclusivity generally does not cover an innovation already approved for another drug product containing the same active moiety or active moieties. A drug product may, however, qualify for exclusivity for an aspect that differs from the earlier-approved drug product, thus providing a continued exclusivity incentive – albeit one that is typically narrower in effect – for manufacturers to conduct new clinical investigations of previously approved drugs. In this way, the Agency's interpretation encourages both further innovation and expansion of what is known about a drug.

ii. Characteristics that Further Define Scope of Exclusivity

Because the 3-year exclusivity provisions of the Hatch-Waxman Amendments entail a balance

[89] 21 CFR 314.108(a). *See* 59 Fed. Reg. 50338, 50357 (Oct. 3, 1994) ("The phrase 'essential to the approval' suggests that the clinical investigations that warrant exclusivity must be vital to the application or supplement . . . '[T]o qualify for exclusivity, there must not be published reports of studies other than those conducted or sponsored by the applicant, or other information available to the agency sufficient for FDA to conclude that a proposed drug product or change to an already approved drug product is safe and effective.'" (internal citations omitted)); 1989 Proposed Rule at 28900 ("In addition, there must not be an already approved drug product for which the applicant could submit an ANDA or 505(b)(2) application. . . . A study will not be considered essential to approval merely because it was necessary for the applicant to conduct the study to avoid the exclusivity of the pioneer and obtain an immediate effective date of approval.").

between innovation and competition, the Agency considers whether certain characteristics of the eligible product, supported by new clinical investigations essential to the product's approval, may further define the scope of its innovation (i.e., the scope of its exclusivity) and thus may be appropriately protected from competition.

This assessment requires the Agency to make a fact-specific determination. The Agency does this by determining whether the relevant characteristics of the drug studied are clinically meaningful (for example, as opposed to merely reflecting the conditions under which the study was conducted). In making this assessment, the Agency may consider a characteristic to be *clinically meaningful* for purposes of 3-year exclusivity if, for example, it significantly changes the population or use for which the drug is appropriate with respect to previously approved drugs with the same active moiety, or would otherwise be expected to change a clinician's determination as to whether the product is appropriate for use in a particular patient.

This assessment is made by FDA's medical and scientific staff based on FDA's understanding of the drug product, the indication or condition the drug is intended to treat, the clinical context of its use, its mechanism of action, and other relevant factors. The scope of an exclusivity-eligible product's innovation is generally cabined by characteristics that affect these clinically meaningful dimensions. Specific characteristics of a product could define the scope of its exclusivity where, for example, these reflected details of the new clinical investigations essential to approval that the Agency determined were clinically meaningful.

At the same time, a particular clinical investigation may be more limited in scope or more specific than the conclusions (and thus the scope of exclusivity) that can be drawn from it. As a result, a drug studied in very specific conditions might be approved with a broader indication and not limited to those conditions under which it happened to be studied.[90] The scope of a product's innovation similarly might not be defined by specific characteristics of its clinical studies where these are not clinically meaningful. Thus, the conditions of approval to which exclusivity applies are the product's innovation for which new clinical investigations were essential, as defined by clinically meaningful characteristics of the product supported by the new clinical investigations essential to its approval.

III. DISCUSSION

This section applies the framework described above to the analysis of whether 3-year exclusivity recognized for Sublocade under section 505(c)(3)(E)(iii) of the FD&C Act bars approval of Brixadi Monthly and Brixadi Weekly. The analysis applies the above-described framework for identifying the scope of a product's innovation. It also explains the Agency's conclusion that

[90] See, e.g., FDA, Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry (July 2018) (hereafter, Indications and Usage Draft Guidance), at 3 ("In some cases, FDA's expert reviewers may fairly and responsibly conclude, based on their scientific training and experience, that the available evidence supports approval of an indication that is broader or narrower in scope than the precise population studied.").

previous exclusivity decisions related to Probuphine and Astagraf XL are consistent with the Agency's decision regarding Sublocade.

A. Effect of Sublocade's Approval on Brixadi

Sublocade is eligible for 3-year exclusivity. An application for a drug containing a previously approved active moiety is eligible for 3-year exclusivity if the approval of the application is supported by at least one (1) new (2) clinical investigation (other than a bioavailability study) (3) that is conducted or sponsored by the applicant and is (4) essential to the approval of the application.[91] Studies RB-US-13-0002 and RB-US-13-0001 were new clinical investigations (other than bioavailability studies) that were "essential to the approval of the [Sublocade] application" and "conducted or sponsored by" the applicant within the meaning of section 505(c)(3)(E)(iii) of the FD&C Act and the implementing regulations in 21 CFR 314.108.

As explained above, FDA's determination of the scope of Sublocade's 3-year exclusivity under section 505(c)(3)(E)(iii) involves two steps. Under the first step, FDA focuses on the drug at issue. For a single entity drug to be potentially barred by 3-year exclusivity for another drug, the drug must contain the same active moiety as the drug with 3-year exclusivity. Sublocade and Brixadi are both single-entity drugs that contain the same active moiety, buprenorphine. Thus, Brixadi's approval has the potential to be barred by Sublocade's 3-year exclusivity, and we must consider the second aspect of the scope inquiry concerning Sublocade's "conditions of approval" supported by the new clinical investigations.

As noted above in section II.B., although the FD&C Act and implementing regulations do not define "conditions of approval," when one or more drugs with the same active moiety have been previously approved, the Agency interprets the scope of 3-year exclusivity for a new approval (new product or supplement to an existing product) to cover the new approval's innovation as compared to previously approved drug products containing the same active moiety for which the underlying new clinical investigations were essential to the approval. Accordingly, to determine the scope of exclusivity for Sublocade, the Agency must determine the innovation(s) for which new clinical investigations were essential to the approval, and for which 3-year exclusivity should be recognized. This innovation must be assessed relative to previously approved drug products containing the same active moiety. The previously approved buprenorphine products are Buprenex (NDA 018401), Subutex (NDA 020732), Butrans (NDA 021306), Belbuca (NDA 207932), and Probuphine.[92] Although there is no exclusivity currently listed for these products, the previous approval of these products may narrow the scope of exclusivity for Sublocade because an aspect of Sublocade's approval may already have been established by these previous approvals (for example, certain clinical investigations might be determined not to be essential to Sublocade's approval because they merely reestablish something that has been shown by the

[91] The approval of an NDA or supplement to an NDA includes approval of labeling submitted in the NDA or supplement. 21 CFR 314.50.

[92] Although all of these products have the same active moiety, the active ingredient for Belbuca, Buprenex, Subutex, and Probuphine is the hydrochloride salt form of buprenorphine, while the active ingredient for Butrans, Sublocade and Brixadi is the free-base form of buprenorphine.

previous approvals).

To determine the scope of 3-year exclusivity for Sublocade, the Agency assessed Sublocade's innovation relative to Probuphine and other previously approved buprenorphine products. Specifically, the Agency asks what unique clinical question(s) about the safety and/or efficacy of the active moiety for the relevant use the new clinical investigations essential to approval answer for the first time. The Agency also considers whether particular characteristics of Sublocade, supported by the new clinical investigations essential to its approval, are clinically meaningful such that they may further define the scope of its innovation.

1. Sublocade's Conditions of Approval

As noted above, at the time of Sublocade's approval, buprenorphine had been previously approved as the active moiety in Buprenex (NDA 018401), Subutex (NDA 020732), Butrans (021306), Belbuca (NDA 207932), and Probuphine. Buprenex was initially approved as a parenteral product for the treatment of moderate-to-severe pain. Buprenorphine was later developed as a treatment for opioid dependence and was approved in Subutex as a sublingual tablet.[93] Buprenorphine was subsequently approved as a transdermal system (Butrans) and as a buccal film (Belbuca), both for the treatment of pain.[94] Most recently, buprenorphine was approved as a 6-month subdermal implant in Probuphine for the treatment of opioid dependence in certain patients who are stable on low-to-moderate doses of a transmucosal buprenorphine product.

The Agency identifies the aspect of Sublocade that is innovative against the background of these prior approvals. FDA started by asking what unique, previously unanswered clinical question(s) about the safety and/or efficacy of buprenorphine for the relevant use (that is, treatment of moderate-to-severe OUD) the new clinical investigations essential to Sublocade's approval answered. Based on a review of the relevant data and information, we conclude that the unique question answered by the studies conducted by Indivior was whether a depot formulation of buprenorphine was effective for treatment of moderate-to-severe OUD over a month-long period. In particular, the CDTL review explained that Studies RB-US-13-0001 and RB-US-13-0002 were required to ensure that the "amount of buprenorphine provided, and the proposed dosing interval were suitable to support the proposed indication" (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).[95]

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[93] Buprenorphine has also been approved for use in combination with naloxone as a sublingual tablet (Suboxone, NDA 20733), a sublingual film (Suboxone, NDA 22410), a buccal film (Bunavail, NDA 205637), and another sublingual tablet (Zubsolv, NDA 204242).

[94] See also May 25, 2016 Memorandum from the CDER Exclusivity Board re: The Scope of Exclusivity for Belbuca, NDA 207932.

[95] NDA 209819, CDTL Review, at 12. Study RB-US-13-0002 demonstrated that following 300 mg subcutaneous injection of the drug product, "Drug Liking" scores measured after challenge with 6 mg or 18 mg of hydromorphone intramuscular injections were not liked better than those measured after challenge with a placebo injection. This data was used to determine the dosage of buprenorphine for Study RB-US-13-0001, which demonstrated that the drug product blocks the effects of exogenously administered opioids for the entire inter-dose period.

Further, a review of previous approvals demonstrated that the studies were not necessary to establish the efficacy of buprenorphine in the treatment of moderate-to-severe OUD generally, because the prior approval of Subutex demonstrated effectiveness of buprenorphine in the treatment of OUD. Moreover, the studies were not necessary to demonstrate efficacy of a depot formulation of buprenorphine in the treatment of OUD generally. Instead, the record indicates that the studies were required specifically to determine the effective dose and dosing interval for a *monthly* depot formulation of buprenorphine so as to deliver an appropriate amount of buprenorphine for the treatment of patients with moderate-to-severe OUD, which had not previously been established by prior approvals.

The studies did not demonstrate that different dosing intervals would be effective, or that the product was effective in treating patients other than those with moderate-to-severe OUD; as a result, Sublocade's exclusivity does not extend beyond this dosing interval and patient population.

2. Characteristics Relevant to Sublocade's Innovation

The Agency also considered whether specific characteristics of Sublocade supported by the new clinical investigations essential to its approval further define the scope of its innovation. As explained above, this is based on FDA's determination as to whether such characteristics are *clinically meaningful*.

First, we note that Sublocade was approved for use in patients who had initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days. This reflects the specific characteristics of Study RB-US-13-0001, in which subjects were initiated with Suboxone sublingual film for 3 days followed by a 4- to 11-day dose-adjustment period.[96] The initiation and dose-adjustment period were necessary to avoid the potentially serious risk of precipitated withdrawal. Sublocade's studies did not demonstrate that it would be safe and effective in patients who had not previously been initiated on any amount of buprenorphine for any period of time. In the Agency's judgment, the fact that use of Sublocade requires a patient to have previously initiated treatment with a different buprenorphine product to address the withdrawal risk is clinically meaningful, in that it would be expected to change a clinician's determination as to whether Sublocade is appropriate for use in a particular patient. At the same time, we conclude that the specific manner by which Sublocade addresses this risk (including the precise length of the initiation and dose-adjustment periods and the nature of the dosage form or formulation used during the lead-in period) does not itself define the scope of its innovation, including because FDA does not believe that these details limit the use of Sublocade before or after this initiation/dose-adjustment to a distinct patient population, nor does this specific initiation/dose-adjustment period create a clinically distinct patient population for which Sublocade is safe and effective. The fact that patients have had a week of dose-adjustment does not cause them to be a distinct patient population. In essence, the Agency concludes that the general requirement to initiate treatment with a different buprenorphine product is clinically

[96] NDA 209819 CDTL Review, at 33.

meaningful because it addresses a safety concern of precipitated withdrawal for buprenorphine products, but the precise manner in which this initiation procedure is conducted is not clinically meaningful.[97]

FDA also considered whether the fact that Sublocade was studied in patients who were new-to-treatment (after initiation) was clinically meaningful such that the scope of Sublocade's innovation should be limited to use in that group and would not extend to patients who were already stable. We conclude that this characteristic of Sublocade's studies does not define the scope of its exclusivity, including because it does not actually constrain the population for which use of Sublocade is appropriate. The Agency's medical and scientific experts determined that the studies in new entrants to treatment supported approval in both groups, because new entrants to treatment are considered a more difficult population to treat than patients who are already clinically stable. Thus, the results of the Sublocade clinical studies extend to clinically stable patients. In contrast, with respect to OUD, studies in stable patients would generally not support approval in new-to-treatment patients. We note that our conclusion that the population studied in Sublocade's trials does not constrain the scope of its innovation would likely be different if the trials had been conducted only in stable patients. In that case, we would expect the limitation to be clinically meaningful based on the likelihood that the studies alone would not, without more information, support use in the more difficult to treat new-to-treatment patients. [98]

In addition, we considered whether Sublocade's innovation was defined by its use of a 300 mg initiation dose and 100 mg strength, or by the administration sites used (i.e., limited to rotating abdominal sites). In the Agency's judgment, neither of these characteristics would be expected to significantly change the population or use for which the product is appropriate, or to change a clinician's determination as to whether Sublocade is appropriate for use in a particular patient. The Agency considered, in particular, whether the 300 mg initiation dose would be expected to represent a barrier to use such that it might significantly change the population for which the product is appropriate. FDA does not believe this is the case. The 300 mg dose is not expected to present significant tolerability problems in new-to-treatment patients with moderate-to-severe OUD who have completed an initiation and dose adjustment period on another buprenorphine product to address the risk of precipitated withdrawal.[99] The peak serum concentration after the first 300 mg dose of Sublocade is lower than the peak concentration for a 16 mg/day sublingual dose, the target dose to which patients new to buprenorphine treatment are typically titrated. More generally, the strength approved for Sublocade was determined to be the appropriate amount of buprenorphine over a one-month dosing interval for the indication.

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[97] The exclusivity analysis might result in a different outcome for a monthly buprenorphine product to treat OUD for which no initiation at all was necessary.

[98] The Agency has recommended that such studies "would support a claim of reduction in risk of relapse but would not support a claim of efficacy in new entrants to treatment." See FDA's Guidance for Industry, "Opioid Use Disorder: Developing Depot Buprenorphine Products for Treatment," (February 2019) (hereafter, "Opioid Use Disorder Guidance"), at 4.

[99] Beginning treatment with a 300 mg dose of Sublocade is also not expected to present tolerability issues for patients transitioning from established treatment with sublingual buprenorphine, even at moderate doses.

The Agency also concludes that Sublocade's use of rotating injection sites is not a clinically meaningful characteristic. This merely reflects aspects of the relevant clinical studies; use of a different injection site would not be expected to make the product appropriate for a different population or use, or to change a clinician's judgment regarding appropriateness of the product for use in a particular patient.

For the above reasons, the Agency concludes that the innovation represented by Sublocade is the effective delivery of buprenorphine in a depot formulation to treat moderate-to-severe OUD over a month-long period in patients who have initiated prior treatment with a buprenorphine product.

3. Determination that Brixadi Monthly Is Blocked by Sublocade's Exclusivity

Based on Sublocade's innovation and the characteristics relevant to Sublocade's innovation, we next examine whether Sublocade's exclusivity blocks the approval of either Brixadi Weekly or Brixadi Monthly.

Like Sublocade, the proposed indications stated in Brixadi's tentatively approved labeling (which apply to both Brixadi Weekly and Brixadi Monthly) also require dose-adjustment on a buprenorphine-containing product to address the risk of precipitated withdrawal, although the details of initiation differ from those of Sublocade.[100] The DOSAGE AND ADMINISTRATION section provides specific instructions for initiating Brixadi *Weekly* in new entrants to treatment, but the instructions for Brixadi *Monthly* provide only for use in patients already being treated with buprenorphine for some period of time, like Sublocade, to protect against precipitated withdrawal.[101]

Because the Agency concludes that the specific details of Sublocade's dose-adjustment and initiation protocol do not define the scope of its innovation (but rather are only one form of a requirement for initiation and dose adjustment with another buprenorphine product to avoid precipitated withdrawal), any differences between the types of initiation used for Sublocade and Brixadi Monthly do not cause Brixadi Monthly to fall outside the scope of Sublocade's exclusivity. Moreover, the different initiation protocol used for Brixadi Weekly (and described in the combined labeling for Brixadi Weekly and Brixadi Monthly) is irrelevant to the question of whether Brixadi *Monthly* is blocked by exclusivity recognized for Sublocade. The differences in labeling between Sublocade and Brixadi Monthly reflect the fact that the studies submitted to support the Sublocade and Brixadi applications took different approaches to initial doses of buprenorphine to address the issue of precipitated withdrawal. In all of the clinical studies submitted to support the Brixadi application, treatment in new entrants to treatment (not already

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[100] Braeburn has proposed a more limited indication for Brixadi Monthly, including in a January 16, 2019 letter to FDA ("Labeling Discussion Doc for FDA 1-15-19.doc"). In relevant part, the indication would state that the monthly product is "indicated for patients who are currently stable on a transmucosal buprenorphine product, or the weekly regimen of BRIXADI."

[101] The tentatively approved Brixadi labeling states that, "because the doses of buprenorphine provided by BRIXADI at doses providing effective blockade of exogenous opioids are higher than doses of [sublingual buprenorphine] typically used to initiate treatment, there is a risk that precipitated withdrawal, a clinically serious condition, could occur if BRIXADI is initiated without a titration period."

on buprenorphine) was initiated with dose titration on Brixadi Weekly, not Brixadi Monthly; no Brixadi studies included initiating treatment on Brixadi Monthly without a dose-adjustment period.[102]

Like Sublocade, Brixadi Monthly was not studied in (and was not demonstrated to be safe and effective for use in) patients who have not completed an initiation and dose adjustment period to avoid precipitated withdrawal.[103] In fact, the Agency concluded that postmarketing clinical trials should be conducted for both Sublocade and Brixadi to study how they could be safely initiated without a period of titration.[104] While the combined Brixadi Weekly and Brixadi Monthly application originally sought approval for both formulations for use in patients who had not previously been initiated and dose-adjusted on a buprenorphine-containing product, and for use in patients with a history of abusing substances other than opioids, it did not establish that Brixadi Monthly is safe and effective for use in patients who have not completed an initiation and dose adjustment period with buprenorphine (either Brixadi Weekly or sublingual buprenorphine), or that Brixadi Monthly could be safely initiated in patients not already being treated with buprenorphine. The original Brixadi application also did not establish that either Brixadi formulation was safe and effective for use in patients with a history of abusing substances other than opioids. Because the Brixadi clinical studies only established that Brixadi Monthly is safe and effective for use in patients initiated and dose-adjusted on a buprenorphine-containing product (including clinically stable patients), the patient population for which Brixadi Monthly is tentatively approved (pending expiry of Sublocade's exclusivity) is the same as that for which Sublocade is approved.

Braeburn has argued that "the ability of long-term stable patients to transition to one of [Brixadi Weekly's or Brixadi Monthly's] several dose-proportional weekly or monthly strengths permits physicians to better individualize the treatment program based upon clinical judgment regarding patient tolerability and clinical efficacy."[105] We note that the way in which Brixadi was studied limits the conclusions that can be drawn regarding potential benefits of its wider range of doses. The Agency is not persuaded at this time based on the information that Braeburn has provided to date that low doses of Brixadi would necessarily provide an advantage of greater flexibility for patients who are already on treatment with low doses of a different buprenorphine product. Because we determine that Sublocade's approved strength is not a characteristic that defines the scope of its innovation, differences in the strength of Brixadi Monthly do not remove it from the scope of Sublocade's exclusivity.

As explained above, the Agency concludes that the innovation represented by Sublocade is the

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[102] Brixadi's Prescribing Information recommends a one-week titration period beginning with a 4-mg test dose of transmucosal buprenorphine (as a screen for precipitated withdrawal), followed by 16 mg of Brixadi Weekly and additional doses of 8 mg Brixadi Weekly as needed in the first week (to achieve the 24-32 mg blockade dose).

[103] Brixadi's proposed labeling states: "Initiating treatment with BRIXADI as the first buprenorphine product has not been studied. Initiating treatment with BRIXADI (monthly) in new entrants to treatment has not been studied."

[104] *See* Approval Letter, NDA 209819, SUBLOCADE (Nov. 30, 2017); Tentative Approval Letter, NDA 210136, BRIXADI (Dec. 21, 2018).

[105] *See* July 23, 2018 letter.

effective delivery of buprenorphine in a depot formulation to treat moderate-to-severe OUD over a month-long period in patients who have initiated prior treatment with a buprenorphine product. This result aligns with the Agency's conclusion that, while Brixadi Monthly and Sublocade are different in certain respects, the products are appropriate for use in the same patient population, and the differences between the two are not clinically meaningful. Further, to the extent there are differences between Brixadi and Sublocade that are clinically meaningful, those differences relate to Brixadi Weekly, not Brixadi Monthly. Differences in the initiation protocol for Sublocade and Brixadi arise from the different ways in which the two products were studied. Specifically, they reflect the ways in which different sponsors independently developing monthly buprenorphine formulations approached the same problem, i.e., mitigating the risk of precipitated withdrawal.

The clinical studies supporting approval of Sublocade, a monthly formulation, did not establish that buprenorphine could be effectively and safely delivered over a weekly period. The Agency considers the distinction between a weekly and monthly depot product to be clinically meaningful. One reason for this is the fact that a prescriber reasonably might want flexibility in dosing period to correspond to the frequency of consultations appropriate for a given OUD patient.[106] Therefore, Brixadi Weekly would not be blocked by Sublocade's unexpired exclusivity.

B. Probuphine and Astagraf XL

The Agency's conclusion regarding the scope of Sublocade's exclusivity is consistent with the Agency's prior exclusivity determinations relating to Probuphine and Astagraf XL. Below, we explain how FDA's determination in each case is consistent.

As initially explained in the February Decision Letter, FDA concluded that the scope of Probuphine's exclusivity was limited by its use in a specific, defined population (generally, certain patients who are already stable on a low dose of buprenorphine).[107]

The Probuphine application initially proposed Probuphine's use in a broader population including new entrants to treatment for a population that would include moderate-to-severe

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[106] In the February Decision Letter, the Agency also addressed arguments raised by Braeburn in its July 23, 2018 letter suggesting that Brixadi Weekly and Brixadi Monthly should be treated as an "integrated system", and that as a result its application could not be blocked by exclusivity covering Brixadi Monthly alone. *See* February Decision Letter, at 33. As explained there, the Agency does not agree that the two products function as an "integrated system" that cannot be treated as two separate products. Use of the monthly product is not dependent on use of the weekly product, or vice versa. The Agency again concludes that there is nothing in the data submitted with the Brixadi NDA to indicate that the Brixadi Weekly cannot be used independently of Brixadi Monthly. Furthermore, the single controlled study (HS-11-421) evaluated the efficacy of Brixadi as an integrated system; the blockade study only used the weekly (HS-13-478) and the open-label study (HS-13-499) allowed the clinician to use either the weekly or monthly formulation.

[107] The Agency described Probuphine's exclusivity as being for use of a single-entity buprenorphine subdermal implant product for a 6-month period, for the maintenance treatment of opioid dependence in patients who have achieved and sustained clinical stability on low-to-moderate doses of a transmucosal buprenorphine containing product.

OUD. Data submitted by the sponsor did not support approval for this use. The sponsor subsequently submitted additional data to demonstrate that Probuphine is effective in a narrower subset of patients: those who are already clinically stable for a sustained period on low to moderate doses of transmucosal buprenorphine. In particular, the relevant study evaluated efficacy of Probuphine for maintenance treatment in patients who were clinically stabilized on 8 mg or less of sublingual buprenorphine.[108] The narrow scope of exclusivity recognized for Probuphine reflected the nature of the population studied. The Agency concluded that the characteristics of the population studied were clinically meaningful and thus necessitated a limitation on the population for which the product was appropriate, and therefore further defined the scope of the exclusivity recognized for the product.

One reason for this is that the conclusion from the study essential to Probuphine's approval could not be extrapolated to new-to-treatment patients. As the Agency has explained, because new entrants to treatment are considered harder to treat than stable patients, studies conducted in *stable* patients (like Probuphine's PRO-814 Efficacy Study) would "support a claim of reduction in risk of relapse but would not support a claim of efficacy in new entrants to treatment."[109] Stable and new-to-treatment patients are distinct in ways that are significant, including because new-to-treatment patients are more difficult to treat. The Agency's determination that Probuphine's exclusivity was limited to use in patients stabilized on a low dose sublingual buprenorphine is based on its medical and scientific judgment about the importance of these characteristics in describing a distinct population.

The Agency's analysis with respect to Sublocade applies the same principle, in that it also focusses on whether a characteristic of the drug product is clinically meaningful for purposes of 3-year exclusivity. FDA concludes that the scope of Sublocade's exclusivity is not defined by use in patients who were subject to the particular initiation protocol described in its approved labeling (i.e., initiated treatment with a transmucosal buprenorphine product, followed by a dose adjustment for a minimum of 7 days). This is because the details of the specific initiation protocol described in the product's labeling are not what matters; what is clinically meaningful is that steps should be taken prior to use of the product to prevent precipitated withdrawal. The product labeling describes one approach to preventing precipitated withdrawal, as supported by the Sublocade studies. However, there are other approaches that could be taken to prevent precipitating withdrawal. As such, this aspect of Sublocade's product labeling does not describe a specific patient population to whom use of the drug should be limited. In contrast, the characteristics of Probuphine for use only in patients already stable on low doses of Probuphine is clinically meaningful because, in the Agency's judgment, it defines the population and use for which it is appropriate (that is, it excludes new entrants to treatment and patients who have not achieved and sustained prolonged clinical stability on low doses of buprenorphine because the studies submitted did not establish that Probuphine would be effective in these populations). In sum, the Agency concludes that Sublocade's exclusivity is not limited by its particular dose-adjustment period because this characteristic was not expected to significantly change the population or use for which it was appropriate—that is, treatment of patients with moderate-to-

[108] NDA 204442 Exclusivity Summary, May 24, 2016.

[109] *See* Opioid Use Disorder Guidance, at 4.

severe OUD who have initiated prior treatment with a buprenorphine product.

The Agency's exclusivity determination with respect to Astagraf XL also reflects the Agency's application of principles consistent with those applied in the Sublocade analysis. Astagraf XL was approved in 2013 based on two Phase 3 controlled clinical trials that were conducted in *de novo* kidney transplant patients.[110] Based on those studies, Astagraf XL was approved for "the prophylaxis of organ rejection in patients receiving a kidney transplant."[111] The Agency determined that the studies conducted for the Astagraf XL application were necessary to support approval of the use of that product in *de novo* kidney transplant patients and that, as a result, this condition of approval was protected by 3-year exclusivity.[112]

A subsequent application, Envarsus XR, was determined to be partially outside the scope of Astagraf XL's exclusivity because its once-daily, ER dosage form of tacrolimus was for the prophylaxis of organ rejection in kidney transplant patients *converted from* tacrolimus immediate-release formulations, in combination with other immunosuppressants, in addition to a proposed use in *de novo* kidney transplant patients.[113] The Agency concluded that conversion use is a different "condition of approval" from the *de novo* use for which Astagraf XL received exclusivity and that Astagraf XL did not conduct new clinical investigations essential to its approval for the conversion use.[114] In reaching this conclusion, the Agency noted that separate clinical studies are needed to support approval in *de novo* patients and conversion patients because the populations, and their inherent risks and goals, are different.[115] In other words, the Agency concluded based on differences in the nature of the populations that the study of only *de novo* patients in connection with Astagraf XL's approval was clinically meaningful because it would be expected to change a clinician's determination as to whether the product is appropriate for use in a particular patient, and, thus, a characteristic that further defined the scope of exclusivity granted to Astagraf XL.

In contrast, as explained above, the fact that Sublocade was studied only in new-to-treatment patients (following initiation) did not represent a clinically meaningful limitation that would constrain the scope of its exclusivity. Although Sublocade's studies only included new entrants to treatment, Sublocade's studies supported the broader indication (both new and stable patients), because new-to-treatment patients with OUD are considered more difficult to treat and thus if the

[110] Astagraf XL Division Director Review at 4.

[111] Astagraf Labeling, Indications and Usage Section.

[112] NDA 206406/Envarsus XR Exclusivity Memo, at 29.

[113] Id. at 46. Note that Envarsus XR was within the scope of Astagraf XL's exclusivity to the extent it sought approval in *de novo* kidney transplant patients.

[114] Id.

[115] Id. at 4. The *de novo* patients start with intense induction regimens consisting of three to four drugs at the time of kidney transplant with the goal of achieving a customized optimum balance between efficacy and toxicity. Clinical studies in *de novo* patients are designed to evaluate the efficacy and safety of the immunosuppressive regimen in providing adequate protection against rejection. In contrast, the goal for studies conducted in conversion patients is to assess the safety and efficacy of conversion because there is a risk of an adverse outcome anytime an alteration, including a change in the immunosuppressive regimen, occurs. Patients who are at least 3 months post transplantation can be enrolled in these conversion studies. Id.

drug is shown to be appropriate for the new-to-treatment patients following initiation, it also would be appropriate for stable patients. In addition, Sublocade and Brixadi Monthly did not address different patient populations with their approaches to initiating treatment; each was addressing the challenge of avoiding precipitated withdrawal in a population not already stable on buprenorphine.

IV. CONCLUSION

For the reasons described above, the Agency concludes on reconsideration that 3-year exclusivity for Sublocade bars approval of Brixadi Monthly prior to November 30, 2020, but it does not block approval of Brixadi Weekly.

If you have any questions, call Matthew Sullivan, Supervisory Regulatory Health Project Manager, at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesiology, Addiction Medicine
and Pain Medicine
Office of Neuroscience
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cc: Indivior

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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