GOODWIN

Scott M. Lassman
+1 202 346 4134
SLassman@goodwinlaw.com

Goodwin Procter LLP
901 New York Avenue NW
Washington, DC 20001

goodwinlaw.com
+1 202 346 4000

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VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Citizen Petition Requesting the Food and Drug Administration ("FDA") to Revoke Orphan Drug Designation for Sublocade (Buprenorphine Extended-Release) Injection for Treatment of Opiate Addiction in Opiate Users

Dear Sir or Madam:

On behalf of Braeburn, Inc. ("Braeburn"), the undersigned hereby submits this Citizen Petition pursuant to 21 C.F.R. §§ 10.30 and 316.29 and section 526 of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 360bb, to request the Commissioner of Food and Drugs to revoke orphan drug designation ("ODD") for Sublocade (buprenorphine extended-release) injection for treatment of opiate addiction in opiate users (currently referred to as opioid use disorder ("OUD")). Such action is necessary to (1) preserve the integrity of the Orphan Drug Act against inappropriate, unintended and abusive "evergreening" tactics, and (2) prevent such tactics from stifling the development and marketing of innovative new buprenorphine treatments to combat the growing opioid epidemic. The foundation of this request is based on the following critical factors:

- Sublocade is not now, nor was it ever, a *bona fide* orphan drug, particularly since more than two million Americans currently are afflicted by opioid addiction.

- Sublocade, which is expected to be a "blockbuster" drug with peak sales of more than $1 billion per year, nevertheless received ODD from FDA. FDA's decision appears to be based on an informal policy allowing the Agency to rely solely upon a *prior ODD decision for a different drug product made nearly 25 years ago.*

- FDA's prior decision, which was based upon a "cost recovery" analysis for the drug Subutex (buprenorphine sublingual tablets), relied upon inaccurate information and unreasonable assumptions provided by the sponsor, Indivior[1], that turned out to be wildly

[1] Many of the actions described in this petition were performed by Indivior's predecessors, Reckitt & Colman Pharmaceuticals, Inc. and Reckitt Benckiser Pharmaceuticals. For ease of reference, this petition will refer to all of these entities collectively as "Indivior."

inaccurate. If reasonable and fair assumptions had been made, Subutex would not have been eligible for ODD in 1994.

- Moreover, because those assumptions were known to be false as early as 2000, two years before Subutex was approved, ODD should have been revoked at that time. In any event, because those assumptions are now known to be false, it would be contrary to the statute, as well as completely irrational, to rely upon them today to award ODD to Sublocade.

- Indivior already received seven years of orphan drug exclusivity ("ODE") for Subutex; nevertheless, it now appears to be seeking a second, successive ODE period for Sublocade based upon the same ODD and relying on 1994 (inaccurate and non-current) data. Granting ODD or ODE to Sublocade under these circumstances would violate the intent of Congress to provide special incentives only to *bona fide* orphan drugs and to prevent inappropriate evergreening.

- More importantly, granting a period of ODE to Sublocade would have devastating public health consequences by blocking any and all future buprenorphine products from coming to market for 7 years (no earlier than December 2024) – *in the middle of one of the worst opioid epidemics in U.S. history*. This would also result in monopoly pricing. Such an outcome would represent an historic abuse of the Orphan Drug Act.

I. Executive Summary

Prior to 1983, pharmaceutical companies did not routinely invest in research for drugs to treat rare diseases because the patient populations were too small for such drugs to be profitable. The Orphan Drug Act was enacted in 1983 to promote the prompt availability of drugs for rare diseases by providing special incentives to sponsors, such as grants, exemptions from fees and testing requirements, and, most significantly, seven years of exclusive marketing.

To qualify for these incentives, a drug must be intended to treat a "rare disease or condition," which is most commonly defined as a disease or condition that affects less than 200,000 patients in the United States. In highly unusual circumstances – of which there have been only three instances in the 35 years since the inception of the Orphan Drug Act in 1983 – a drug may qualify if it affects more than 200,000 Americans but there is "no reasonable expectation" the sponsor will recover the costs of developing and marketing the drug.

Sublocade does not qualify as an orphan drug under either prong. First, it is intended for the treatment of OUD, a disease that affects several million patients in the United States. Second, by Indivior's own admission Sublocade is expected to be highly profitable. Indivior forecasts that net revenues will be in the range of $50 million to $70 million for fiscal year 2019, and the company "remains confident" of peak annual net revenue of more than $1 billion, which would make Sublocade a "blockbuster." Because the current marketplace already provides adequate incentives for development of Sublocade in terms of huge expected profits, Sublocade is not eligible for the special incentives reserved for *bona fide* orphan drugs.

Sublocade nevertheless has been designated as an orphan drug because of a well-meaning but ultimately harmful administrative policy adopted by FDA. This informal policy allows Sublocade to "piggy-back" on the ODD granted to another drug in 1994 – *nearly 25 years ago*. In essence, FDA considers Sublocade and the other drug, Subutex, to be the "same drug" because they both contain buprenorphine. Accordingly, FDA transferred the ODD granted to Subutex in 1994 to Sublocade nearly 25 years later (without considering the underlying eligibility or appropriateness of Sublocade as an "orphan drug").

The basis for FDA's original grant of ODD to Subutex, however, was highly unusual – and highly specific to Subutex and the marketing conditions it expected to face in the mid-1990s. The vast majority of the clinical development program for Subutex was paid for with taxpayer dollars via large grants from the National Institute of Drug Abuse ("NIDA"). Despite this significant government funding, or thee fact that FDA had a "significant concern" that the intended patient population was estimated to be between 1,000,000 and 1,500,000 in 1993, FDA nonetheless granted ODD to Subutex based on Indivior's assertions that there was "no reasonable expectation" it would recover the costs of developing and marketing Subutex during the first seven years after approval. This 1993 assertion, which turned out to be wildly inaccurate, has absolutely no relevance to whether Sublocade, which was approved nearly 25 years later, qualifies as an orphan drug in 2019. By applying the 1994 ODD to Sublocade even though the cost recovery analysis focused solely on Subutex, FDA's decision not only is arbitrary and capricious, but also violates the statutory provision requiring it to consider all sales of the relevant "drug" in the United States. *See* 21 U.S.C. § 360bb(a)(2)(B).

Moreover, the 1994 designation decision itself was unjustified and unreasonable, as evidenced by the more than $285 million in sales enjoyed by Indivior since the original approval of Subutex in 2002. This was due, in large part, to the fact that Indivior provided FDA with inaccurate and misleading information. While Indivior was telling FDA that the market for buprenorphine would be severely restricted for the foreseeable future (*i.e.*, limited to use in methadone clinics), the company was making business decisions, including extensive lobbying plans, based upon the expectation that the market for buprenorphine could and would expand significantly within a few years. These plans crystallized in 2000 – two years prior to Subutex's approval in 2002 – with passage of the Drug Addiction Treatment Act ("DATA 2000"), a law that was drafted by Indivior and enacted with significant lobbying assistance from the company. Accordingly, if reasonable and fair assumptions had been made – assumptions that Indivior itself was relying upon at the time to run its business – Subutex would not have been eligible for ODD in 1994. In any event, it was clear in 2002 when Subutex was approved that the 1994 assumptions were unreasonable, at which time ODD should have been revoked.

In light of this history, Braeburn was dismayed to learn from FDA that Sublocade may be granted ODE, which could prevent any other buprenorphine product intended to treat OUD from coming to market until December 30, 2024. This would be a major mistake not only because Sublocade obviously does not qualify as a *bona fide* orphan drug, but also because *Indivior already obtained and used its ODE for Subutex (and Suboxone) from 2002 through 2009 to generate extraordinary and long-dated financial returns*. Incredibly, Indivior now appears to be seeking a second, successive exclusivity period for Sublocade based upon the same 1994 ODD

that triggered the first exclusivity period for Subutex. This is a blatant attempt to abuse the orphan drug system by engaging in inappropriate and offensive "evergreening" of ODE, contrary to the intent of Congress.

If FDA grants ODE, it would have a devastating impact on the public health, and is completely inconsistent with the well stated goals of FDA and the US Government to expeditiously increase access to a wider range of therapies to address one of the worst public health crises in United States history. According to the Centers for Disease Control and Prevention, almost 400,000 people died from an opioid-related overdose from 1999 to 2017 – nearly 50,000 in 2017 alone – and those numbers are escalating. To combat this crisis, the federal government has recognized that new and better treatment options are needed, especially in relation to increased access, and use, of buprenorphine. For its part, the FDA issued a final guidance document in 2019 to promote the development of innovative treatments for OUD, particularly buprenorphine products that can be administered as long-acting implants or injectable depots.

A decision to grant ODE to Sublocade will completely frustrate these goals by effectively freezing the development of new buprenorphine products for the treatment of OUD – *until approximately 2025*. This is because ODE is broad, preventing FDA from approving not just generic copies of Sublocade, but also *any* product intended for the same use that contains buprenorphine. While sponsors theoretically could avoid exclusivity by making a showing of "clinical superiority," this showing is unpredictable and often requires expensive head-to-head, comparative clinical trials, thereby fundamentally "lifting the regulatory bar" beyond a showing of safety and effectiveness for any sponsor seeking marketing approval for buprenorphine. As a practical matter, therefore, an award of ODE would effectively strangle investment in innovative OUD treatments containing buprenorphine for the foreseeable future, contrary to the expressed policies of FDA, HHS and the White House. This would severely limit competition and treatment options and result in monopoly pricing for a critical drug needed to fight the opioid epidemic.

FDA, however, has the tools and authority to avoid these consequences. For the reasons discussed below, Sublocade is not now and never has been eligible for ODD. Accordingly, FDA should use its authority to revoke Sublocade's ODD pursuant to 21 C.F.R. § 316.29(a) and concomitantly refuse to grant, or revoke, ODE. These actions will protect the integrity of the Orphan Drug Act by rejecting transparent evergreening tactics for products that do not qualify as *bona fide* orphan drugs. More importantly, it will maintain robust incentives for companies to invest in new and innovative treatment options for OUD patients to combat the ongoing opioid crisis, consistent with federal objectives. The grounds for this request are set forth in detail below.

II. Actions Requested

For the reasons that follow, Braeburn respectfully requests the Commissioner to:

1. Revoke the orphan drug designation granted to Sublocade (buprenorphine) for treatment of opiate addiction in opiate users (currently referred to as OUD); and

2. Refuse to grant orphan drug exclusivity to Sublocade, or withdraw such exclusivity, if already granted.

III. Statement of Grounds

A. Legal and Factual Background

1. The Orphan Drug Act

The Orphan Drug Act is intended to provide special incentives for the development of drugs intended to treat rare diseases that otherwise would not be developed. These incentives include research grants, tax credits, waived FDA user fees and protocol assistance. *See, e.g.*, 21 U.S.C. § 360ee. In addition, the Orphan Drug Act provides a particularly valuable seven-year period of exclusive marketing, known as Orphan Drug Exclusivity or ODE, for designated orphan drugs that are approved by FDA. *Id.* § 360cc.

To qualify for many of these incentives, a sponsor must request that its drug be "designated" by FDA as a drug for a "rare disease or condition," *i.e.*, an orphan drug. *Id.* § 360bb. The term "rare disease or condition" is defined by the statute as a disease or condition that:

- affects less than 200,000 patients in the United States ("Patient Population Prong"); or

- affects more than 200,000 but for which there is "no reasonable expectation" that the costs of developing and marketing the drug will be recovered from sales of the drug in the United States ("Cost Recovery Prong").

Id. § 360bb(a)(2). A request for designation must be submitted to FDA *before* the submission of the application for the proposed orphan drug. *Id.* § 360bb(a)(1). An orphan drug that is both designated and approved is eligible for ODE. *Id.* § 360cc.

In recent years, however, FDA appears to have adopted an informal policy that allows *certain* sponsors to transfer the ODD granted to one drug to a subsequent version of that drug *without* submitting: (a) a separate request for ODD per 21 C.F.R. § 316.20; or (b) a "plausible

hypothesis" of clinical superiority.[2] This informal policy has been exclusively applied where both the new and prior drug products are sponsored by the same company. In such situations, FDA automatically bestows the ODD that was granted to the first product to any subsequent product that contains the same active moiety and is intended for the same use as the first product (without even the briefest or most cursory re-assessment). FDA has explained that this policy is justified because ODD applies to the active moiety, not a specific drug product.[3]

Although this policy is briefly mentioned on FDA's website, it is not set forth or explained in any FDA regulation or guidance document. Moreover, it is unclear when it was adopted, since FDA has applied it in some recent cases (*e.g.*, Orenitram) but not in other older situations (*e.g.*, Nutropin Depot, Tyvaso) (see discussion in section III.B.2 below). The precise scope of FDA's informal policy, therefore, is unclear. However, it does not seem to incorporate any time limits between ODD transfers. In other words, as far as Braeburn can tell, FDA will transfer ODD regardless of how long ago (or on what basis) the original ODD was granted, and irrespective of any other considerations or intervening developments.

2. <u>Subutex</u>

Subutex is a sublingual tablet formulation of buprenorphine (NDA 20-732) approved on October 8, 2002. It was developed with substantial funding and assistance from the federal government, particularly NIDA. Together with a related product called Suboxone (buprenorphine/naloxone), also approved on October 8, 2002, Subutex was the first buprenorphine drug product approved for "the treatment of opioid dependence."[4]

Approximately eight years before its approval – on June 15, 1994 – Subutex was designated by FDA as an orphan drug for "opiate addiction in opiate users."[5] The designation was unusual because it was based on the Cost Recovery Prong, not the Patient Population Prong. Since 1983, only three drugs appear to have received ODD based upon the Cost Recovery Prong (and two of those are Subutex and Suboxone). As noted above, Subutex could not meet the requirements of the Patient Population Prong because, at the time (early 1990's), FDA estimated that the number of "opioid addicts" in the United States exceeded one million patients, which is well above the statutory threshold of 200,000 patients.[6]

Accordingly, FDA granted ODD to Subutex based on its determination that there was "no reasonable expectation" that the cost of developing and marketing buprenorphine for "opiate addiction in opiate users" would be recovered from sales of the drug in the United States (FDA

[2] To obtain ODD for a new version of a drug that contains the same active moiety and is intended for the same use as a previously-approved drug (*i.e.*, is "otherwise the same"), a sponsor must provide a "plausible hypothesis" that the second-in-time drug is clinically superior to the previously approved drug. 21 C.F.R. §§ 316.20(a), 316.25(a)(3).
[3] *See* Def.'s Response to Pl.'s Mot. Summ. J. and Cross-Mot., *United Therapeutics Corp. v. HHS*, Civ. Action No. 17-1577, p. 13 (Dec. 22, 2017) (Exhibit 1).
[4] *See* Subutex Prescribing Information, INDICATIONS AND USAGE (2002), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/20732,20733lbl.pdf
[5] Letter from Marlene Haffner, M.D., M.P.H. to Charles O'Keeffe, Executive Vice President, Reckitt & Colman Pharmaceuticals, Inc. (June 15, 1994) (Exhibit 2).
[6] FDA ODD Review for Subutex, p. 3 (June 25, 1993) ("1993 ODD Review") (Exhibit 3).

made the determination despite the fact that NIDA had borne a substantial portion of the development costs). FDA's determination relied upon several important assumptions and limitations. First, the analysis only considered revenue expected to be generated during the first seven years of marketing of Subutex (with an initially estimated approval date of 1995).[7] Second, it assumed that existing requirements that limited the use of narcotics to certain treatment centers (*e.g.*, methadone clinics) would not be liberalized prior to Subutex's approval or, indeed, during the life of the product. This assumption, in turn, supported assumptions that the pricing options for Subutex and the size of the available patient population likewise would be severely circumscribed.[8]

As discussed further below in section III.B.3, these assumptions were not reasonable when made and, not surprisingly, turned out to be highly inaccurate. This was due, in large part, to enactment of DATA 2000 on October 17, 2000.[9] DATA 2000 effectively negated all assumptions put forward by Indivior about the limited market for buprenorphine by exempting buprenorphine from the severe restrictions that applied to other narcotics, such as methadone. DATA 2000 thus significantly changed the marketplace for buprenorphine, thereby dramatically improving the financial prospects of Subutex and Indivior's ability to expeditiously earn oversized economic returns (in excess of its investment). Moreover, despite its assertions to FDA that the marketplace restrictions were unlikely to be changed during the life of Subutex, Indivior was instrumental in conceiving and passing DATA 2000 *prior to the approval of Subutex* (see section III.B.3.a below).

Because it was designated as an orphan drug, Subutex was granted a seven-year period of ODE upon its approval in 2002. That exclusivity period expired on October 8, 2009.[10] Because of the changes to the law wrought by DATA 2000, Subutex became an extremely profitable drug for Indivior. Between 2003 and 2007, Subutex prescriptions increased rapidly from approximately 9,000 per year to approximately 192,000 per year, which paralleled equally rapid increases in sales from approximately $1 million in 2003 to approximately $42,780,000 in 2007.[11] Indeed, during the approximately nine years it was marketed (between 2002 and 2011), Subutex generated net revenue in the United States of over $285 million.[12] When combined with Suboxone sales, which also received ODD and ODE pursuant to the Cost Recovery Prong, Indivior reported more than $2.3 billion in net revenue generated from Subutex and Suboxone in the United States, (not including sales from 2002 and 2003).[13] Together, Subutex and Suboxone became two of Indivior's most profitable products and represent the two largest and most successful products in the history of the treatment of OUD.

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[7] FDA ODD Review for Subutex, p. 4 (June 14, 1994) ("1994 ODD Review") (Exhibit 4).
[8] 1994 ODD Review, p. 5 ("It is reasonable to assume that there will be virtually no change in the treatment-seeking population, or that any positive shift will be incremental.").
[9] Pub. L. No. 106-310, § 3501 et seq., 114 Stat. 1101 (2000).
[10] FDA Database, Orphan Drug Designations and Approvals, accessed April 3, 2019 (Exhibit 5).
[11] Mark T, Kassed C, et al. Alcohol and Opioid Dependence Medications: Prescription Trends, Overall and by Physician Specialty. Author manuscript published in final edited form as: *Drug Alcohol Depend*. 2009 January 1; 99 (1-3): 345-349. Doi:10.1016/j.drugalcdep.2008.07.018 ("Mark & Kassed Article") (Exhibit 6).
[12] Data on file (derived from Indivior Annual Reports and Symphony Health Solutions Integrated Sales Audits).
[13] *Id*.

3. Sublocade

Sublocade is an extended-release, injectable depot formulation of buprenorphine approved for "the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of seven days."[14] When Sublocade is injected into the body, it forms a solid depot that is intended to release buprenorphine over a one-month period. Indivior, the sponsor of Subutex, submitted a 502(b)(2) application for Sublocade (NDA No. 209819) on May 30, 2017, and FDA approved Sublocade six months later on November 30, 2017.

According to FDA's Orphan Drug Database ("Database"), Sublocade is currently designated as an orphan drug for "[t]reatment of opiate addiction in opiate users."[15] The Database further states that this designation was granted on June 15, 1994. Since Sublocade did not exist in 1994, Sublocade's ODD appears to be based on FDA's original designation of Subutex as an orphan drug in 1994. In other words, FDA appears to have applied the informal policy described above solely because Sublocade and Subutex contain the same active moiety (buprenorphine) and are both owned by Indivior. Based on the information in FDA's Database, Braeburn does not believe Indivior submitted a separate ODD request for Sublocade.[16] Perhaps most alarmingly (and surprisingly given the obvious changes to the market landscape and the explosion of the opioid crisis), FDA does not appear to have done any assessment to re-confirm that Sublocade is a *bona fide* "orphan drug" that needs or deserves the special incentives under the Orphan Drug Act.

FDA's publication entitled *Approved Drug Products With Therapeutic Equivalence Codes*, commonly referred to as the Orange Book, currently indicates that Sublocade qualifies for 3-year exclusivity under the FFDCA, with an exclusivity code of "NP" (New Product) that expires on November 30, 2020.[17] Although Sublocade was approved more than 16 months ago, the Orange Book does not indicate that Sublocade has been awarded ODE. Nevertheless, Braeburn has been informed that FDA currently is considering whether or not to award ODE to Sublocade. Under the Orphan Drug Act, Sublocade is not eligible for ODE unless it is "clinically superior" to previously approved buprenorphine drugs. 21 U.S.C. § 360cc(c). Although Braeburn does not believe Sublocade meets this high standard, there is no guarantee that FDA will agree with Braeburn's analysis.[18]

[14] Sublocade Prescribing Information, § 1 (Nov. 2017), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209819s001lbl.pdf.
[15] FDA Database, Orphan Drug Designations and Approvals, accessed April 3, 2019 (Exhibit 5).
[16] Braeburn submitted a Freedom of Information Act ("FOIA") request for such information and will supplement this Petition if it receives relevant documentation regarding a standalone ODD request for Sublocade.
[17] FDA Electronic Orange Book, Sublocade, accessed April 3, 2019 (Exhibit 7).
[18] Braeburn reserves its right to address "clinical superiority" and similar issues related to ODE in a separate submission to FDA. This Petition does not address three-year exclusivity for Sublocade in any way.

B. FDA Should Revoke Orphan Drug Designation for Sublocade

FDA should not award seven years of exclusive marketing to Sublocade in reliance on a 25-year-old ODD decision that was itself based on inaccurate and potentially misleading information for a different drug product that already received its seven years of ODE and which ultimately generated outsize economic returns for its sponsor. Nor should it award such exclusivity under these circumstances in the middle of one of the worst opioid epidemics in U.S. history. Such an outcome would represent an historic abuse of the Orphan Drug Act.

Not surprisingly, the grant of ODE to Sublocade is not compelled by either the statute or the regulations. On the contrary, FDA has ample authority – and justification – to revoke Sublocade's ODD and thereby prevent it from obtaining a seven-year exclusivity period it clearly does not deserve.

FDA's longstanding regulations give the Agency the power to revoke ODD if:

1. the request for designation contained an "untrue statement of material fact;"
2. the request "omitted material information" required by the regulations; or
3. "FDA subsequently finds that the drug in fact had not been eligible for orphan-drug designation at the time of submission of the request therefor."

21 C.F.R. § 316.29(a). For an ODD based on the Cost Recovery Prong, revocation can be based upon new information collected after the ODD decision – or even after approval – demonstrating that the drug product actually is profitable and thus that the initial economic assumptions were not reasonable.[19] Here, for the reasons described below, FDA has grounds to revoke Sublocade's ODD based upon all three criteria. Accordingly, FDA should immediately act to revoke the ODD for Sublocade.

1. Sublocade Is Not Eligible for ODD Under the Orphan Drug Act

FDA should revoke ODD because Sublocade is not, and never was, qualified as an orphan drug under the statute. As noted above, the Orphan Drug Act requires a drug to meet one of two criteria to qualify as an orphan drug: the Patient Population Prong or the Cost Recovery Prong. Sublocade does not satisfy the requirements of either prong.

First, Sublocade is intended to treat a disease – OUD – that affects *millions* of patients in the United States. In 1993, FDA estimated that the total number of patients in the United States addicted to opioids was between 1,000,000 and 1,500,000 and thus "easily exceeded" the 200,000 patient threshold required under the statute.[20] Since then, the opioid epidemic has been fueled by prescription drug abuse, including oxycodone and fentanyl. In 2014, the Substance Abuse and Mental Health Services Administration ("SAMSHA") estimated that almost 2.3

[19] *See* FDA ODD Review for Raloxifene (Evista), p. 13 (May 20, 2005) (recognizing that FDA's regulations allow revocation based on sales occurring after approval) (Exhibit 8).
[20] 1993 ODD Review, p. 3.

million people aged 12 years and older abused or were dependent on opioids, up from almost 1.7 million in 2005.[21] Accordingly, OUD is certainly not a rare disease, and Sublocade therefore clearly does not satisfy the Patient Population Prong.

Second, Sublocade is expected to be highly profitable. Indivior forecasts that net revenues will be in the range of $50 million to $70 million for fiscal year 2019.[22] Moreover, the company has consistently reinforced that peak annual net revenue for Sublocade would exceed $1 billion. As recently as December 18, 2018, Indivior stated that it "remains confident" of this prediction.[23] Based on the company's own assessment, therefore, Sublocade is expected to be a highly profitable drug that clearly does not satisfy the Cost Recovery Prong.

Despite these conspicuous factual and statutory deficiencies, which confirm that buprenorphine is no longer a *bona fide* orphan drug, FDA nevertheless granted ODD to Sublocade. Although the basis for FDA's decision is not explained in the Database, given the June 15, 1994 designation date, it appears that FDA is allowing Sublocade to piggy-back on the ODD granted to Subutex approximately 25 years ago. Specifically, FDA appears to be relying on the regulatory fiction that Sublocade is the "same drug" as Subutex (because both contain buprenorphine) and thus that Subutex's 1994 ODD can be "grandfathered" or otherwise transferred to Sublocade twenty-five years later – without a new ODD request or FDA review under the statutory and regulatory standards.

For the reasons discussed below, FDA's informal ODD transfer policy cannot be applied to Sublocade. Although such transfers may be consistent with FDA's general policy of granting ODD "liberally,"[24] as applied here, the ODD transfer is unduly liberal and conflicts with the underlying goals of the Orphan Drug Act and the explicit statutory and regulatory requirements applicable to the designation process. As such, Sublocade's ODD should be revoked.

First, FDA's ODD "transfer policy" permits the designation of drugs that are not *bona fide* orphan drugs. Congress included a designation process in the Orphan Drug Act specifically "to assure that the financial incentives and other regulatory provisions of the bill apply only to drugs for rare diseases and conditions."[25] Indeed, the primary purpose of the Orphan Drug Act is "to provide incentives to develop promising drugs for rare diseases or conditions *that would not otherwise be developed and approved*."[26] By circumventing the designation process for new versions of previously designated drugs, FDA's informal policy creates a loophole through which drugs that do not presently satisfy either the Patient Population Prong or the Cost Recovery Prong nevertheless can reap the special benefits of ODD, including the possibility of ODE. In this case, for instance, Sublocade received ODD despite the fact it is expected to be a

[21] GAO Report, *Opioid Addiction: Laws, Regulations, and Other Factors Can Affect Medication-Assisted Treatment Access*, p. 2 (Sept. 27, 2016) (GAO-16-833), *available at* https://www.gao.gov/products/GAO-16-833.
[22] Indivior Financial Results, p. 2 (Feb. 14, 2019) (Exhibit 9).
[23] Indivior Legal and Trading Update, p. 2 (Dec. 18, 2018) (Exhibit 10).
[24] *See* 56 Fed. Reg. 3338, 3340 (Jan. 29, 1991) ("On the whole, FDA would liberally grant orphan-drug designation when the threshold prevalence or profitability tests are met.").
[25] H.R. Rep. No. 97-840, p. 8 (1982).
[26] 76 Fed. Reg. 64,868, 64,870 (emphasis added).

blockbuster drug that treats a patient population numbering in the millions. Because market conditions already provide adequate incentives for the development of Sublocade, it should not be eligible for the special incentives reserved for *bona fide* orphan drugs.

Second, FDA's policy facilitates perpetual evergreening of exclusivity. Congress has expressed strong concerns over the years – including in recent years – that companies could abuse the orphan drug system by seeking designation for drugs with significant commercial value "solely to get market exclusivity that would cut off competitors who might also seek approval of the drug."[27] FDA's informal policy exacerbates this problem by permitting infinite, successive seven-year periods of ODE based upon a single ODD determination – even when the subsequent versions of the original drug are highly profitable. Here, for example, Subutex has already enjoyed a seven-year period of ODE together with enormous financial returns beginning in 2002 based on the original ODD granted in 1994. Now, Indivior is seeking a second, successive exclusivity period for Sublocade based upon the same ODD that triggered the first exclusivity period, despite the fact that Sublocade is expected to be a "blockbuster" drug and notwithstanding that the costs incurred to develop buprenorphine over twenty years ago have been recovered many times over. This is a blatant attempt to abuse the orphan drug system by engaging in inappropriate "evergreening" of ODE, contrary to the intent of Congress.

FDA's longstanding policy has been that ODE is "used up" or "spent" if the same drug already has been approved for the same orphan indication.[28] FDA thus will not award a second exclusivity period to the same drug, a position Congress recently affirmed when it amended the Orphan Drug Act to include a "clinical superiority" requirement. FDA should apply the same policy to ODD and consider Indivior's 1994 ODD to have been "used up" or "spent" once Subutex's ODE was triggered. As such, it should not be available for "re-use" by Sublocade to seek a second, successive exclusivity period or for evergreening by future drug products.

Third, FDA's informal policy does not constitute "reasoned decision-making" because it allows the Agency to ignore any and all factors *most relevant* to a designation decision, *i.e.*, current information about patient population and cost recovery. This permits an absurd "one-and-done" assessment by FDA on orphan drug *bona fides*, notwithstanding that, as is the case here, more than two decades have passed since the initial designation assessment. In this case, the cost recovery analysis performed in 1994 for Subutex has absolutely no bearing on whether Sublocade (or buprenorphine) meets the relevant statutory requirements to qualify as an orphan drug today.

Worse, the 1994 decision was based upon assumptions about the marketplace that changed radically in 2000 after passage of DATA 2000 – *well before the approval of Subutex*. Those changes made Subutex extremely profitable and, as projected by Indivior, promise to transform Sublocade into a "blockbuster" drug with peak annual revenue exceeding $1 billion. FDA cannot remain "blind" to this information, or ignore fundamental and obvious marketplace changes, and thereby grant ODD to Sublocade based upon historical data and assumptions that

[27] H.R. Rep. No. 100-473, p. 6 (1987).
[28] Nutropin Depot (ProLease) ODE Review, p. 2 (June 6, 2000) (Exhibit 11).

are nearly 25 years old and, in hindsight, clearly inaccurate. To do so would be arbitrary and capricious in violation of the Administrative Procedure Act.[29] 5 U.S.C. § 706(2)(A).

Fourth, FDA's policy fails to establish reasonable time limits between ODD transfers. Here, FDA is allowing Sublocade to piggy-back on a designation decision that is *almost 25 years old*. There is nothing to prevent similar ODD transfers for drugs approved 50, 100 or even 500 years from now. This is inherently unreasonable and will create ODD "perpetuities" that provide permanent benefits to their holders regardless of whether the future products qualify as *bona fide* orphan drugs. In similar situations, FDA has imposed time limits to prevent a grant of ODD based upon stale and outdated information to drugs that no longer qualify as orphan drugs. *See* 21 C.F.R. § 316.24(a).[30] If FDA included similar time limits (*e.g.*, one year) for transfers of ODD, its policy might be reasonable; in this case, however, the nearly 25-year gap is unreasonable and fails to account for the dramatic marketplace changes - and resultant enormous financial windfalls - that have occurred between 1994 and today (and which clearly negate the appropriateness of providing orphan incentives to any subsequent drugs for OUD).

Finally, FDA's policy violates the statute when applied in the specific context of the Cost Recovery Prong. In making a cost recovery determination, the statute directs FDA to consider "sales in the United States of *such drug*" – without any limitation as to time period. 21 U.S.C. § 360bb(a)(2)(B) (emphasis added). In this case, however, FDA's analysis was limited to the first seven years of expected sales of buprenorphine (*i.e.*, 1995 through 2002) – a time period that could not and did not account for any "sales" of Sublocade.[31] FDA nevertheless appears to have applied ODD to Sublocade on the grounds that it is the "same drug" as Subutex.

FDA cannot have it both ways. If ODD applies to the "active moiety" broadly, then the statutory cost recovery analysis must be equally broad and account for all reasonably anticipated sales of "such drug," which in this case includes Sublocade. In the alternative, if FDA limits the cost recovery analysis to the first seven years of sales (as it did here in accordance with its regulations),[32] then ODD likewise must be limited to the specific "such drug" covered by that assessment (*i.e.*, Subutex). By applying the 1994 ODD broadly to Sublocade even though its cost recovery analysis was focused narrowly on expected sales of Subutex, FDA's decision violates the statutory provision requiring it to consider all "sales in the United States of *such drug*." *Id*. (emphasis added).

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[29] *Motor Vehicle Mfrs. Assn. of United States, Inc. v. State Farm Mut. Automobile Ins. Co.*, 463 U.S. 29, 43 (1983) (internal citations omitted) (an agency decision is arbitrary and capricious if it "has relied on factors which Congress has not intended it to consider, *entirely failed to consider an important aspect of the problem*, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.") (emphasis added).

[30] In that case, FDA has recognized that granting ODD when circumstances change "may be inconsistent with the purpose of the Orphan Drug Act, to provide incentives for the development of drugs for 'rare diseases or conditions …'" 76 Fed. Reg. 64,868, 64,872 (Oct. 19, 2011). FDA was particularly concerned that ODD could be granted to drugs even if patient prevalence increased beyond 200,000 over time. To minimize this risk, FDA imposed a time limit of one-year for sponsors to respond to ODD deficiency letters.

[31] 1994 ODD Review, p. 14.

[32] 21 C.F.R. § 316.21(c).

2. Sublocade Is Not Eligible for ODD Under the Orphan Drug Regulations

FDA should revoke the ODD for Sublocade for the independent reason that, on information and belief, Indivior never submitted a new request containing a "plausible hypothesis" that Sublocade is superior to previously approved buprenorphine products.[33]

Under FDA's regulations, if a drug is "otherwise the same" as a previously approved drug for the same rare disease or use, the sponsor must present a "plausible hypothesis" that the new drug "may be clinically superior to the first drug." 21 C.F.R. § 316.20(a). If the sponsor fails to submit a "medically plausible hypothesis for the possible clinical superiority of the subsequent drug," FDA must refuse to grant ODD. *Id*. § 316.25(a)(3). A drug is considered to be the "same drug" if it contains the same active moiety and is intended for the same orphan indication as the previously approved drug. *Id*. § 316.3(b)(14)(i). This special rule is intended to protect the value of ODE, prevent inappropriate evergreening, and ensure the prompt approval of therapeutically superior drugs.[34]

In this case, Sublocade is "otherwise the same" as Subutex because both products are single-ingredient buprenorphine drugs intended for the treatment of opiate dependence and addiction, *i.e.*, OUD. Accordingly, under FDA's regulations, Indivior was required to submit a "plausible hypothesis" of Sublocade's superiority. *Id*. § 316.20(a). However, on information and belief, Indivior never complied with this requirement and instead obtained ODD by piggybacking on the designation previously granted to Subutex in 1994. Because Sublocade did not satisfy the clear requirements set forth in FDA's regulations, it was never eligible for ODD.

In accordance with the informal policy described above, FDA appears to have ignored the "plausible hypothesis" requirement for Sublocade because it is the "same drug" as Subutex and thus automatically eligible for ODD.[35] But this reasoning is circular: even if Sublocade and Subutex are considered to be the "same drug," *FDA's regulations apply to this very situation*. FDA has explained that "[i]n the absence of a clinical superiority hypothesis, the Agency does not interpret the Orphan Drug regulations to permit designation of a drug that is otherwise the same as a drug that is already approved for the same use. …"[36] Put more succinctly, "absent such a hypothesis, designation can be neither sought nor obtained."[37]

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[33] Braeburn bases this assertion on that fact that FDA identifies June 15, 1994 as the date Sublocade was designated as an orphan drug. This strongly suggests that Indivior did not submit a separate ODD request but instead is relying upon Subutex's ODD. If Indivior did, in fact, submit a separate ODD request for Sublocade prior to submission of the Sublocade NDA that contained a "plausible hypothesis" of clinical superiority, Braeburn hereby withdraws this argument. Braeburn has submitted a FOIA request for the relevant records on any ODD requests for Sublocade and will update this Petition, if warranted, when we receive a response.

[34] FDA Petition Response to CSL Behring, FDA-2011-P-0213, p. 4 (Aug. 8, 2012).

[35] As noted above, FDA's informal policy is mentioned briefly in briefs filed in the UTC case. *See* Def.'s Response to Pl.'s Mot. Summ. J. and Cross-Mot., *United Therapeutics Corp.*, Civ. Action No. 17-1577, p. 13 (Dec. 22, 2017).

[36] 78 Fed. Reg. 35,117, 35,122 (June 12, 2013).

[37] Letter from Gayatri R. Rao, M.D., J.D., Director, FDA Office of Orphan Products Development, to Philip Katz, Esq., p. 14 (Nov. 13, 2012) (Exhibit 12).

Significantly, the regulations do not distinguish between types of sponsors with respect to this requirement, exempt, or otherwise provide preferential treatment to a sponsor if it developed both drugs at issue. This broad coverage makes sense because the clinical superiority requirement is essential to fostering the overriding goals of the Orphan Drug Act and to preventing evergreening. FDA has explained that if the same drug has already been approved for the orphan disease or condition,

> designation would be inappropriate [in the absence of a clinical superiority hypothesis] because it would be inconsistent with the primary purpose of the Orphan Drug Act, which is to provide incentives to develop promising drugs for rare diseases or conditions that would not otherwise be developed.[38]

In addition, FDA has warned that without a plausible hypothesis of clinical superiority, "permitting orphan-drug designation of a drug that is already approved for the orphan indication could permit inappropriate 'evergreening' of exclusive approval periods."[39] Of course, both of these concerns apply with equal force regardless of whether the drugs at issue have been developed by different sponsors or by the same sponsor. Indeed, the example of "inappropriate evergreening" described in the FDA quote above involves a single sponsor.

In the past, FDA has enforced its "clinical superiority" regulation even where the drugs at issue were developed by the same company. For example, FDA required Genentech to provide a plausible hypothesis that Nutropin Depot, a sustained-release formulation of human growth hormone, was clinically superior to Nutropin, Genentech's previously-approved, immediate-release formulation of human growth hormone.[40] Likewise, FDA refused to grant ODD to Tyvaso, United Therapeutics Corporation's ("UTC's") inhalation formulation of treprostinil, until the company demonstrated that Tyvaso was clinically superior to Remodulin, the company's IV formulation of treprostinil.[41] Although FDA appears to have changed its policy in subsequent cases (*e.g.*, Orenitram), Braeburn submits that the above examples followed the proper process and are more consistent with clear regulatory requirements and goals of the Orphan Drug Act than FDA's new informal policy.

Finally, FDA's recently-adopted policy is arbitrary and capricious because it treats similarly-situated sponsors differently.[42] Existing sponsors can receive ODD for new drug products without any showing of clinical superiority or demonstration that the new product still qualifies as an orphan drug. This allows existing sponsors to reap all of the benefits granted to orphan drugs, including exemptions from user fees and pediatric testing requirements, even if

[38] 76 Fed. Reg. 64,868, 64,870.
[39] *Id*.
[40] Nutropin Depot (ProLease) ODD Review (Apr. 27, 1999) (Exhibit 13).
[41] Letter from Frank Sasinowski to Timothy Cote, M.D., M.P.H., Director of FDA's Office of Orphan Products Developments, p. 1 (July 20, 2009) (referencing FDA letter dated May 5, 2009 denying ODD for Tyvaso because it had not presented a plausible hypothesis of clinical superiority) (Exhibit 14).
[42] *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C. 1997) (recognizing that unjustified differential regulatory treatment of materially identical products is arbitrary and capricious).

their new products do not independently qualify as orphan drugs at the time of subsequent approval. This, in fact, is what happened with Orenitram (treprostinil) extended-release tablets, which was designated as an orphan drug without being required to (a) submit a new designation request, (b) satisfy the Patient Population or Cost Recovery Prongs, or (c) demonstrate a plausible hypothesis of clinical superiority, but nevertheless was exempted from pediatric testing requirements.[43]

New sponsors, by contrast, must meet all statutory and regulatory requirements for ODD at the time of the request, including the Patient Population/Cost Recovery requirements and the "plausible hypothesis of clinical superiority" requirement. If they fail to satisfy applicable requirements, they are not eligible for the special incentives and exemptions available to designated orphan drugs, unlike similarly situated drugs subject to FDA's informal policy. This disparate treatment is unjustified and prejudicial.

3. Subutex Was Not Eligible For ODD In 1994 or 2002

Even if Sublocade is permitted to rely upon the 1994 ODD decision for Subutex, Sublocade's ODD nevertheless must be revoked because *Subutex* was not eligible for ODD in 1994. Moreover, Subutex's designation should have been revoked prior to 2002 based upon known legal and marketplace changes, including passage of DATA 2000, which demonstrated that the assumptions underlying the original ODD request and decision were invalid and inaccurate. In short, Subutex was never eligible for ODD because there was always a "reasonable expectation" that it would recover its costs, and this is clearly supported by the outsize economic returns accruing following approval.

a. The 1994 ODD Was Based Upon Inaccurate Information and Unreasonable Assumptions Provided By Indivior

Indivior submitted its request for ODD in 1993.[44] This submission, however, was filled with inaccurate information and unreasonable assumptions about cost recovery for Subutex. For example, Indivior asserted that Subutex would be approved in 1995.[45] This, however, was an obvious impossibility given that "the IND's had just been submitted in May, 1994, the CRADA has just been formally agreed with NIDA, and 1994 is half over …"[46] The 505(b)(2) application for Subutex, in fact, was not submitted to FDA until March 28, 1997, and was not approved by FDA until 2002 – seven years after Indivior's prediction. By that time, the marketplace for buprenorphine had changed dramatically.

Indeed, the marketplace for buprenorphine factored heavily in Indivior's 1993 assumptions and hypotheses regarding cost recovery. At the time, products such as methadone

[43] Orenitram Approval Letter, p. 2 (Dec. 20, 2013) (exempting Orenitram from pediatric testing requirements because of ODD status) (Exhibit 15).
[44] Subutex ODD Request (Nov. 17, 1993) (Exhibit 16).
[45] 1994 ODD Review, p. 3 (sponsor's submission "included the assumption that the product would be first marketed in 1995.").
[46] 1994 ODD Review, p.4.

and levomethadyl acetate ("LAAM") were subject to significant regulatory oversight by both FDA and the Drug Enforcement Administration ("DEA") and generally restricted to use in a closed system of approved clinics and hospital pharmacies, commonly known as "methadone clinics."[47] In setting forth its cost recovery analysis, Indivior claimed that buprenorphine would only compete with methadone and LAAM within this closed system. It specifically informed FDA that:

- The number of available "treatment slots" was a maximum of 115,000 nationally;
- There were 104,000 patients already being treated in methadone treatment programs, and thus those programs were close to capacity;
- Buprenorphine does not equate to higher dosage levels of methadone, substantially reducing the number of patients who are suitable for or willing to be treated with it;
- Buprenorphine will compete in the same marketplace with methadone and LAAM and is unlikely to achieve any market share at normal margin price (and increasing price would trigger lower market penetration); and
- Subutex would not recover its research and development costs based on expected sales during the first seven years of marketing.[48]

To underscore these points, Indivior represented to FDA that the limitations on treatment slots for narcotics (and thus the number of eligible patients) were "highly unlikely to be modified during the life of the product."[49]

However, at the same time Indivior was telling FDA that legal and marketplace changes for buprenorphine were "highly unlikely," the company was making business decisions based upon the opposite assumption – that such changes "certainly seemed achievable" within five years,[50] well within the life of the product (and, ultimately, well prior to the actual approval of Subutex in 2002). According to Charles O'Keeffe, Executive Vice President of Indivior's pharmaceutical business at the time, Indivior undertook the development of Subutex (and Suboxone) only because "[i]t seemed possible that, under the right circumstances and once approved by the FDA for use in treatment of opioid dependence, buprenorphine might be exempted from some of the burdens associated with the use of methadone and LAAM."[51] Indivior's business plan – which it viewed as "at least a 5-year project" – involved three connected objectives: (a) obtaining ODE, (b) obtaining FDA approval, and (c) changing the laws

[47] *See generally* J. Jaffe, C. O'Keeffe, From morphine clinics to buprenorphine: regulating opioid agonist treatment of addiction in the United States. Drug and Alcohol Dependence. 70: S3-S11 (2003) ("O'Keeffe Article") (Exhibit 17).
[48] Subutex ODD Request, p. 2.
[49] *Id*.
[50] O'Keeffe Article, pp. S7-S8 (Exhibit 17).
[51] *Id*. at S7.

so that buprenorphine would "reach the mainstream practice of medicine."[52] Significantly, Indivior viewed its "legislative effort" to be "inextricably intertwined" with its efforts to obtain FDA approval of Subutex.[53] The available evidence thus strongly suggests that Indivior knew the assumptions it was providing to FDA in 1993 and 1994 were highly inaccurate.

Indivior began its lobbying efforts per its business plan at least as early as 1995, drafting a bill that was a precursor to DATA 2000.[54] Over the next several years, Indivior engaged in extensive lobbying activities to change the legal requirements governing distribution and use of buprenorphine for treatment of opioid addiction.[55] As expected, those lobbying efforts bore fruit in 2000 with passage of DATA 2000. This was not only roughly within the 5-year window predicted by Indivior but, more significantly, *two years prior to approval of Subutex.*

DATA 2000 dramatically changed the "economics of marketing buprenorphine," the benefits of which have largely and exclusively accrued to Indivior in the interim. The Act expanded access to addiction treatment for non-methadone scheduled III, IV and V controlled substances, of which buprenorphine was the only product in development for OUD. The Act also created the "DATA 2000 waiver," which expanded capacity for addiction treatment beyond the "methadone treatment slots" of the narcotic treatment programs to any healthcare practitioner willing to become accredited through an 8-hour educational course. The result of DATA 2000 was the creation of a separate market for OUD treatment known as Outpatient Based Opioid Treatment ("OBOTs"). These OBOTs were not permitted to prescribe methadone and thus had only two FDA approved medications for the treatment of OUD at their disposal: Subutex and Suboxone, both with orphan-protection for 7 years (and both owned by Indivior).

DATA 2000 thus eradicated all assumptions underlying Indivior's claim that there was "no reasonable expectation" it would recover its costs for Subutex. In particular, it rapidly expanded the capacity of OUD treatment to approximately 348,530 available treatment slots in five years (2007) with DATA 2000 waivered healthcare practitioners (3,311 and 2,492 healthcare practitioners, certified for 30 and 100 patients, respectively).[56] And because these DATA 2000-waivered healthcare practitioners did not have authority to prescribe methadone, Subutex and Suboxone were neither tethered to methadone's "high doses" nor its low price.

The results were highly profitable for Indivior: between 2003 and 2007, Subutex sales in the U.S. increased substantially from approximately $1 million in 2003 to approximately $42,780,000 in 2007.[57] During the approximately nine years it was marketed (between 2002 and 2011), Subutex generated net revenue in the United States of over $285 million.[58] When

[52] *Id*.
[53] *Id*.
[54] *Id*. at S8.
[55] *Id*.
[56] Estimates based on data provide by SAMSHA, Number of DATA-Waived Practitioners Newly Certified Per Year, available at https://www.samhsa.gov/medication-assisted-treatment/practitioner-program-data/certified-practitioners.
[57] Mark & Kassed Article, see supra note 12.
[58] Data on file (derived from Indivior Annual Reports and Symphony Health Solutions Integrated Sales Audits).

combined with Suboxone sales, Indivior reported more than $2.3 billion in net revenue generated from Subutex and Suboxone in the United States, (excluding sales from 2002 and 2003, which were not reported in Indivior's annual reports to shareholders).[59] This ultimately enabled a broader buprenorphine sales platform within OUD that has accrued to Indivior's exclusive benefit with billions in sales over nearly two decades.

Braeburn is not suggesting that there is anything wrong with Indivior's lobbying efforts; on the contrary, they significantly benefited OUD patients by expanding treatment opportunities for buprenorphine. But Indivior's plans to expand and liberalize the buprenorphine marketplace through lobbying and other activities – and its views that such regulatory changes were achievable – should have been communicated to FDA because they were material to FDA's cost recovery analysis for purposes of ODD. Indeed, disclosure to FDA of such factors that would obviously "affect the orphan drug status" is mandatory under the annual reporting regulations. 21 C.F.R. § 316.30(c). Instead, Indivior was communicating certain assumptions to FDA (which FDA relied upon) while operating its business on very different assumptions.

Indivior's initial request for ODD thus contained an "untrue statement of material fact" regarding the likelihood of regulatory changes affecting the marketplace for buprenorphine or, at the very least, "omitted material information" regarding such changes. *See* 21 C.F.R. § 316.29. Moreover, it clearly was based upon inaccurate information and unreasonable assumptions and thus failed justify ODD at the time.

b. <u>Subutex's ODD Should Have Been Revoked After Enactment of DATA 2000</u>

Moreover, Subutex's designation should have been revoked once it became clear in 2000 that the assumptions underlying the ODD request were unreasonable and the Cost Recovery Prong was no longer satisfied. But even after passage of DATA 2000, Indivior continued to represent to FDA in annual reports that "[w]e are not aware of any change in the development or marketing plans that will affect the orphan status of either [Subutex or Suboxone]."[60] Braeburn has identified at least three such submissions in November 13, 2000, January 4, 2002, and October 14, 2002. Contrary to Indivior's representations, DATA 2000 obviously and radically changed the "marketing plans" for Subutex and Suboxone by expanding the available patient population, protecting buprenorphine from competition from methadone and LAAM, and giving Indivior more control over pricing.

These misrepresentations to FDA's Office of Orphan Drug Products ("OODP") in 2000 and 2002 were material because FDA could have revoked the 1994 ODD based upon subsequent legal and marketplace developments, particularly given the enactment of DATA 2000. For this reason, FDA's annual report regulations specifically require sponsors to report "any changes that may affect the orphan-drug status of the product." 21 C.F.R. § 316.30(c). While FDA's regulations explicitly state that changes to the size of the relevant patient population cannot

[59] *Id*.
[60] Subutex Orphan Drug Annual Report (Nov. 6, 2000); Subutex Orphan Drug Annual Report (Jan. 4, 2002) (collectively included as Exhibit 18).

trigger revocation, they provide no similar exemption for changes affecting the Cost Recovery Prong. *Id*. § 316.29(c). Accordingly, FDA has reserved the right to revoke ODD if subsequent legal and/or marketplace developments indicate that prior cost recovery assumptions were faulty and/or that there is, in fact, a "reasonable expectation" that a sponsor will recover its costs.

FDA, in fact, stated this proposition explicitly in its ODD decision for raloxifene (Evista), the only other drug designated under the Cost Recover Prong besides Subutex and Suboxone. In that case, FDA required the sponsor to provide FDA with updated information in annual reports – *even after approval* – to "substantiate the assumptions and hypotheses" underlying the initial cost recovery analysis (such as new patents or competitor launches). FDA stated that this additional information was necessary "to determine if the designation and/or marketing exclusivity should remain in place or *whether the designation and/or exclusivity should be revoked as permitted under 21 CFR 316.29.*"[61] Assessing the ongoing applicability of orphan drug status is therefore both a responsibility of FDA and, perhaps more importantly, a reminder that the incentives that are available under the Orphan Drug Act should only be afforded to drug products that are themselves *bona fide* orphan drugs (without reference to earlier drugs or outdated assumptions).

Here, it is clear that the assumptions and hypotheses underlying the 1994 ODD request were inaccurate and unreasonable. There is also evidence that Indivior knew such information was inaccurate but presented it to FDA anyway. If accurate and reasonable assumptions had been made, Indivior could not have shown that there was "no reasonable expectation" it would recover its costs. Accordingly, Indivior was not in fact eligible for ODD for Subutex at the time of the initial request. Moreover, once the legal and marketplace conditions changed after enactment of DATA 2000, Indivior should have informed FDA of this development, and FDA should have revoked Subutex's ODD. For the foregoing reasons, the 1994 ODD for buprenorphine should be revoked now.

C. <u>FDA Should Refuse to Grant ODE to Sublocade (Or Withdraw Such Exclusivity If Previously Granted)</u>

If FDA revokes ODD for Sublocade or Subutex, it should refuse to grant ODE to Sublocade or withdraw such exclusivity if already granted. Under the statute, ODE cannot be granted to a drug unless it has a valid orphan-drug designation. 21 U.S.C. § 360cc(a) (ODE available for "a drug designated under section 526 for a rare disease or condition"). Likewise, FDA regulations provide that, for an approved drug like Sublocade, "revocation of orphan-drug designation also suspends or withdraws the sponsor's exclusive marketing rights for the drug …" 21 C.F.R. § 316.29(b).

[61] FDA ODD Review for Raloxifene (Evista), p. 13 (emphasis added).

1. The United States Is In the Midst of An Opioid Epidemic

Moreover, granting ODE to Sublocade would have a devastating impact on the public health. The United States is in the midst of one of the worst public health crises in its history. According to the Centers for Disease Control and Prevention, almost 400,000 people died from an opioid-related overdose from 1999 to 2017.[62] Opioid overdose deaths are projected to result in 700,000 deaths during the period from 2016 to 2025.[63] In 2017 alone, more than 70,200 people died of a drug overdose, with more than two-thirds of those fatalities—around 68%—attributable to opioid abuse.[64] Troublingly, these numbers are on the rise: in 2017, the number of opioid-related deaths was six times higher than the number in 1999. *Id.* Recent data suggest that more than two million Americans currently suffer from opioid-related substance-use disorders.[65]

The federal government has recognized this escalating crisis and has made addressing the opioid epidemic in America a top priority. On October 26, 2017, the President declared the opioid crisis a Nationwide Public Health Emergency, "mobilizing his entire Administration to address drug addiction and opioid abuse."[66] Likewise, on October 5, 2017, officials from HHS and FDA testified before Congress and reiterated the administration's commitment to addressing the crisis.[67] And as part of its five-point strategy to address the opioid epidemic, HHS has pledged to "[i]mprove access to prevention, treatment, and recovery support services to prevent the health, social, and economic consequences associated with opioid addiction and to enable individuals to achieve long-term recovery."[68]

Consistent with that effort, FDA Commissioner Gottlieb announced in September 2017 that medication-assisted treatment—*i.e.*, the use of medication in combination with counseling and behavioral therapy—"is one of the major pillars of the federal response to the opioid epidemic in this country."[69] On October 25, 2017, during a House hearing on the federal response to the opioid epidemic, Dr. Gottlieb went even further, calling for the expanded use of medication-assisted treatment and explaining that FDA would issue new guidance to manufacturers to promote the development of novel therapies, including ones that treat a wider range of symptoms.[70] FDA issued its final guidance on February 6, 2019.[71]

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[62] Centers for Disease Control & Prevention, *Opioid Overdose: Understanding the Epidemic* (Dec. 19, 2018), https://bit.ly/2jEOHfs.
[63] Q. Chen et al., *Prevention of Prescription Opioid Misuse and Projected Overdose Deaths in the United States*, JAMA Network Open (Feb. 1, 2019), https://bit.ly/2Gr3Krp.
[64] *Id.*
[65] National Inst. on Drug Abuse, *Opioid Overdose Crisis* (Mar. 2018), https://bit.ly/2j6YEE1.
[66] The White House, Press Release, *President Donald J. Trump Is Taking Action on Drug Addiction and the Opioid Crisis* (Oct. 26, 2017), https://bit.ly/2VBqPfU.
[67] *See* S. Comm. on Health, Education, Labor and Pensions, *The Federal Response to the Opioid Crisis: Written Testimony on Behalf of Witnesses from HHS* (Oct. 5, 2017), https://bit.ly/2RHrPjv.
[68] HHS, *Strategy to Combat Opioid Abuse, Misuse, and Overdose* at 3, https://bit.ly/2R5bhPv.
[69] FDA, Press Release, *Statement from FDA Commissioner Scott Gottlieb, M.D., on the Agency's Continued Efforts to Promote the Safe Adoption of Medication-Assisted Treatment for Opioid Addiction* (Sept. 20, 2017), https://bit.ly/2D02WZr.
[70] FDA, Press Release, *Remarks from FDA Commissioner Scott Gottlieb, M.D., as Prepared for Oral Testimony Before the House Committee on Energy and Commerce* (Oct. 25, 2017), https://bit.ly/2FjVxFp.

2. Granting ODE to Sublocade Would Choke Off All Future Investment In New Buprenorphine Drugs for OUD

A decision to grant ODE to Sublocade would completely subvert the federal government's response to the opioid crisis by suffocating future investment in new buprenorphine therapies for the treatment of OUD – *until approximately 2025*. The seven-year period of orphan exclusivity is extremely broad, blocking approval not just of Abbreviated New Drug Applications ("ANDAs"), but also of 505(b)(2) applications and full NDAs – *even for novel products that develop all of their own data*. 21 U.S.C. § 360cc(a). This means that ODE would prevent FDA from approving not just generic copies of Sublocade, or even just buprenorphine depot products generally; rather ODE would prevent FDA from approving *any product* intended for the same use that contains buprenorphine, regardless of dosage form, route of administration or technological features.

Indeed, in a recent example, FDA withdrew approval of drugs in a different dosage form than the drug with ODE simply because they all contained the same active moiety and were intended for the same use. FDA explained that "the scope of Bendeka's *exclusivity extends to all applications containing the same active moiety* as Bendeka, bendamustine, and bars approval of any application containing bendamustine for any exclusivity-protected indication starting on the date of Bendeka's approval for seven years."[72] It is thus clear that the scope of ODE for Sublocade will be expansive.

While a sponsor theoretically could avoid exclusivity by demonstrating that its new buprenorphine product is "clinical superiority" to Sublocade, few, if any, will accept this challenge. FDA's "clinical superiority" determinations are highly discretionary and thus inherently unpredictable. Moreover, FDA often requires expensive head-to-head, comparative clinical trials. This raises the bar significantly beyond what would be required to demonstrate safety and efficacy. As a practical matter, therefore, an award of ODE would effectively strangle investment in innovative OUD treatments containing buprenorphine for the foreseeable future, contrary to the expressed policies of FDA, HHS and the White House. By suppressing competition unduly, it also will allow Indivior to charge monopoly prices for Sublocade. Because of buprenorphine's central role in combatting the raging opioid epidemic, this will have a devastating impact on the public health.

D. Conclusion

For the reasons discussed above, Sublocade is not now and never has been eligible for ODD. Accordingly, FDA should use its authority to revoke Sublocade's ODD pursuant to 21 C.F.R. § 316.29(a) and, concomitantly, refuse to grant, or revoke, ODE. These actions will protect the integrity of the Orphan Drug Act by rejecting transparent evergreening tactics for

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[71] *See* FDA, *Opioid Use Disorder: Developing Depot Buprenorphine Products for Treatment—Guidance for Industry* (Feb. 2019), https://bit.ly/2F3Dmzo ("2019 OUD Guidance").

[72] FDA Letter to Applicants for Certain Products Containing Bendamustine, FDA-2018-N-3773, p. 1 (Feb. 20, 2019).

products that do not qualify as *bona fide* orphan drugs. More importantly, they will maintain robust incentives for companies to invest in new and innovative treatment options for OUD patients to combat the ongoing opioid crisis.

IV. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

V. Economic Impact

Petitioner will submit economic information upon request of the Commissioner.

VI. Certifications

A. Certification under 21 C.F.R. § 10.30[73]

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

Scott M. Lassman
Counsel to Braeburn, Inc.

cc: Elizabeth Dickinson, Office of Chief Counsel
Dr. Janet Maynard, Director, Office of Orphan Product Development
Sharon Hertz, M.D., Director, DAAAP

[73] Braeburn is not submitting the certification set forth in 21 C.F.R. § 10.31(c) because the action requested in this petition, if taken, could not delay approval of any ANDAs, 505(b)(2) applications or 351(k) applications. *See* 21 C.F.R. § 10.31(a)(1). Braeburn, in fact, believes granting this petition would have the opposite effect.