

**Written Testimony before the U.S. House of Representatives,
Energy and Commerce Committee, Health Subcommittee**

Hearing on “Improving Safety and Transparency in America’s Food and Drugs”

Kao-Ping Chua, M.D., Ph.D.

Assistant Professor of Pediatrics

Susan B. Meister Child Health Evaluation and Research Center

University of Michigan Medical School

January 29, 2020

Introduction

Chairwoman Eshoo, Ranking Member Burgess, and Distinguished Members of the Subcommittee: thank for the opportunity to participate in today's hearing.

I am a pediatrician and health policy researcher with expertise in opioid policy and orphan drug policy. These two areas of my research became unexpectedly intertwined when Sublocade, a once-monthly buprenorphine injection, was approved as an orphan drug to treat opioid use disorder. This approval potentially entitled Sublocade to a seven-year period of exclusivity during which no new buprenorphine products could be marketed for opioid use disorder.

I strongly support passing H.R. 4712, the Fairness in Orphan Drug Exclusivity Act, because it will close the loophole that allowed Sublocade's orphan approval, permanently block the possibility of orphan drug exclusivity for Sublocade, and preserve access to buprenorphine for the millions of Americans with opioid use disorder.¹

My testimony will proceed as follows. First, I will explain why ensuring access to buprenorphine is critical to slow the U.S. opioid epidemic. Second, I will explain why Sublocade's orphan approval was an abuse of orphan drug policy. Finally, I will explain what H.R. 4712 does and why it a common-sense step for both opioid policy and orphan drug policy.

Qualifications

To begin, I will briefly review my qualifications to speak as an expert at today's hearing. I am a primary care pediatrician, health policy researcher, and Assistant Professor in the Department of Pediatrics and the Susan B. Meister Child Health Evaluation Research Center at the University of Michigan Medical School. I completed my pediatrics residency at Boston

Children's Hospital and Boston Medical Center, after which I received a PhD in health policy from Harvard University and spent two years as a faculty member at the University of Chicago.

As a doctor, I have been fortunate to have had diverse clinical experiences, including taking care of children with medical complexity in a tertiary children's hospital, serving an inner-city population as an attending in the pediatric emergency department, and working as a primary care pediatrician for a suburban and rural population.

Through my clinical experiences, I have gained a firsthand understanding of the devastating effects of the opioid epidemic on children and young adults, many of whom have lost siblings or parents to opioid overdose or even died of overdose themselves.^{2,3} To prevent these harms, I conduct research that seeks to improve the safety of opioid prescribing to children and young adults.^{4,5} Additionally, using my doctoral training in statistics and policy evaluation, I conduct research that assesses the effects of state and federal policies on opioid prescribing⁶⁻⁸, including opioid prescribing limits that restrict the duration of opioid prescriptions for patients new to opioids.

My clinical experiences also have helped me appreciate the challenges faced by the families of children who suffer from rare orphan diseases, including high out-of-pocket costs for medical care and difficulty obtaining access to expensive orphan drugs due to insurer restrictions. I have conducted research that estimates patients' out-of-pocket costs for orphan drugs, assesses the number of pediatric orphan drugs approved over the last decade, and documents the rising impact of orphan drug spending on the U.S. health care system.⁹

My interests in opioid policy and orphan drug policy converged in the case of Sublocade. In July 2019, I and my co-author Professor Rena Conti (a health economist, Associate Professor

of Questrom School of Business and Associate Research Director of Biopharma & Public Policy for the Boston University Institute for Health System Innovation & Policy) wrote a blog post for *Health Affairs* arguing that Sublocade’s orphan approval represented not only an abuse of orphan drug policy but also a potential catastrophe in the treatment of opioid use disorder.¹⁰ On the basis of this blog post and my research expertise, I received an invitation to speak at today’s hearing.

Buprenorphine: a key weapon against the opioid epidemic

The U.S. opioid epidemic is the worst public health crisis of this generation

The scope of the U.S. opioid epidemic cannot be understated. Over the past decade, the epidemic has claimed the lives of hundreds of thousands of Americans.¹¹ The epidemic has cost society billions of dollars¹² and has been a major contributor to the recent and unprecedented decline in life expectancy in America.¹³ More Americans now die each year from opioid overdose than from car accidents or cancer.¹⁴

Buprenorphine is a safe and effective medication to treat opioid use disorder

Given the scope of the opioid epidemic, it is crucial for policymakers to ensure access to safe and effective treatments for opioid use disorder, also known as opioid addiction. These medications include methadone, extended-release naltrexone, and buprenorphine.¹⁵ While all three of these medications are important, my focus today will be on buprenorphine.

Buprenorphine is a safe treatment for opioid use disorder. As a “partial opioid agonist”, it binds to opioid receptors on the surface of cells in the body, thus decreasing cravings, withdrawal, and the euphoric effects of other opioids that patients may take at the same time.¹⁶ Buprenorphine is generally safer than “full” opioid agonists like methadone because it does not bind to opioid receptors as strongly. Specifically, buprenorphine has a “ceiling effect”, meaning

that its effect tapers off at higher dosages, thus decreasing the risk of overdose if too much is taken.¹⁶

Buprenorphine is also an effective treatment for opioid use disorder. A systematic review of 31 clinical trials found strong evidence that buprenorphine is superior to placebo for retaining patients in treatment for opioid use disorder.¹⁷ Furthermore, this review found that high-dose buprenorphine is superior to placebo and equally as effective as methadone in decreasing use of illicit opioids such as heroin.¹⁷

Because of buprenorphine's favorable safety profile, federal legislation allows it to be prescribed in office-based settings.¹⁵ As a result, buprenorphine is more easily accessed compared to methadone, which can only be accessed by visiting methadone treatment centers in-person.¹⁵

Extended-release formulations of buprenorphine can improve adherence to therapy

Until recently, the only buprenorphine products available were short-acting formulations taken daily, such as Suboxone (buprenorphine-naloxone sublingual film).¹⁵ This changed in May 2016 when the drug company Braeburn Pharmaceuticals received FDA approval for Probuphine, an extended-release buprenorphine implant that lasts six months.¹⁸ In November 2017, the drug company Indivior received approval for Sublocade, a once-monthly extended-release buprenorphine injection.¹⁹ Because extended-release products do not require patients to remember to take buprenorphine every day, they can promote adherence to therapy.^{18,20}

Barriers to buprenorphine access lead to underuse

Despite the fact that buprenorphine is a safe and effective treatment for opioid use disorder, data suggest that it is widely underused. A January 2020 study published in the *Journal*

of the Medical Association showed that while the percentage of the U.S. population receiving buprenorphine increased between 2009 and 2018, this percentage was still far lower than the percentage of the U.S. population with opioid use disorder. Moreover, among adolescents and young adults aged 15-24 years, buprenorphine prescribing rates decreased.²¹

Low buprenorphine use is due to barriers such as stigma, insufficient clinician education, and requirements for clinicians to undergo training and obtain a waiver to prescribe buprenorphine.²² In addition, the high prices of buprenorphine products (**Table**) may create barriers to treatment, including poor medication adherence due to high out-of-pocket costs for patients, as well as cost-related refusal of insurers to cover some buprenorphine products.^{15,23} According to the National Academies of Science, Engineering, and Medicine, overcoming these barriers and increasing buprenorphine use is a key step towards slowing the opioid epidemic.²²

Table. Average wholesale price^a of a 30-day supply of seven buprenorphine products FDA-approved to treat opioid use disorder

Product name	Description	Average wholesale price^b
Probuphine	Extended-release buprenorphine implant	\$5,940
Sublocade	Once-monthly buprenorphine injection	\$1,990
Suboxone	Buprenorphine-naloxone sublingual film ^c	\$180
Zubsolv	Buprenorphine-naloxone sublingual tablet ^c	\$160
Bunavail	Buprenorphine-naloxone buccal film ^c	\$311
Buprenorphine-naloxone	Generic buprenorphine-naloxone sublingual tablets ^c	\$143
Buprenorphine hydrochloride	Generic buprenorphine sublingual tablets ^c	\$124

^aAverage wholesale price is an estimate of the price that retail pharmacies pay to wholesale distributors for a drug. Source: IBM Micromedex.²⁴

^bDisplays the average wholesale price for a 30-day supply of the lowest-strength formulation, with the exception of Probuphine, for which the price of a six-month implant is listed.

^cSublingual tablets are placed under the tongue; buccal films are placed between the gum and cheek

The controversy over Sublocade’s orphan approval

Overview of the Orphan Drug Act

To understand the controversy surrounding Sublocade’s orphan approval, some background on the Orphan Drug Act is needed. This Act was passed in 1983 to incentivize the development of rare disease treatments, which had limited sales potential due to the small number of patients eligible for treatment.²⁵ To receive these incentives, drug companies must first obtain “orphan drug designation” through one of two pathways. By far, the most common pathway is for companies to demonstrate that the drug treats a rare disorder affecting 200,000 or fewer Americans. For drugs that treat a disorder affecting more than 200,000 Americans, designation can be granted if companies demonstrate that there is no reasonable expectation that U.S. sales will be sufficient to recover development and production costs (the “cost-recovery prong”). Once designation is granted, companies receive benefits such as tax credits and grants for clinical testing, as well as a waiver of FDA user fees for drug applications.²⁶

If clinical testing is successful and FDA approves an “orphan indication” for an orphan-designated drug, the company is entitled a seven-year period of “orphan drug exclusivity.” During this period, FDA cannot approve applications by competitors for drugs that contain the same active moiety (active ingredient) and that treat the same condition.²⁶

Under FDA policy, orphan drug designations never expire. Multiple orphan approvals can occur under the same designation provided that the drug contains the same active moiety, treats the same condition, and is developed by the same company. Each of these approvals brings another round of orphan drug exclusivity.²⁷

Sublocade's predecessor, Subutex, obtained orphan drug designation in 1994 under the cost recovery prong

Since the Orphan Drug Act was passed in 1983, the cost-recovery prong has only been used to grant orphan drug designation to three drugs.²⁸ Two of these three drugs were buprenorphine sublingual tablets (Subutex) and buprenorphine/naloxone sublingual tablets (Suboxone), both of which were designated in 1994 to treat opioid use disorder. Reckitt-Benckiser, the drugs' manufacturer and parent company of Indivior, could not obtain these designations via prevalence criteria because opioid use disorder was not a rare disease in 1994, just as it is not today. Rather, Reckitt-Benckiser argued that the drugs would not be economically viable, citing sales projections that assumed that buprenorphine prescribing would only be allowed in the small number of treatment centers that dispensed methadone.¹⁹

The basis for Subutex's orphan drug designation was faulty

In 2000, the Drug Addiction Treatment Act²⁹, legislation for which Reckitt-Benckiser aggressively lobbied¹⁹, allowed buprenorphine prescribing in office-based settings, greatly expanding market size and the potential number of patients eligible for treatment. Both Subutex and Suboxone were approved in 2002 under their 1994 orphan drug designations and received orphan drug exclusivity. Between 2002 and 2011, Subutex generated \$285 million in sales while Suboxone's sales reached billions of dollars¹⁹, figures that controverted the notion that these drugs had limited economic potential.

Subutex's orphan drug designation was grandfathered to Sublocade

Despite this, in November 2017, FDA approved Sublocade under Subutex's 1994 orphan drug designation without requiring another cost-recovery analysis, because both drugs contain

the same active moiety (buprenorphine), treat the same condition (opioid use disorder), and are made by the same company (Indivior spun off from Reckitt-Benckiser in 2014).¹⁹ Thus, Sublocade became the company's third orphan drug for opioid use disorder, even though it did not treat a rare disease and even though the economic viability of buprenorphine products had been demonstrated. Indivior itself predicted that Sublocade will reach \$1 billion in peak annual sales¹⁹, thus negating the possibility that the company could have obtained a new orphan drug designation for Sublocade under the cost recovery prong.

Implications of Sublocade's orphan approval

Sublocade's orphan approval could have needlessly jeopardized the lives of millions of Americans with opioid use disorder

FDA's decision to grandfather Subutex's orphan drug designation to Sublocade meant that Indivior was entitled to a seven-year period of orphan drug exclusivity. If exclusivity were granted, new competing buprenorphine products for opioid use disorder would have been barred from the market until December 2024. Such products included Braeburn Pharmaceuticals' extended-release buprenorphine injection Brixadi, which was tentatively approved by FDA in December 2018.¹⁹

The resulting monopoly for Indivior would not only stifle innovation but would also allow an extended period during which it could charge high prices for Sublocade. The average wholesale price for each monthly dose of Sublocade is currently \$1,991²⁴, a price that has prompted some payers to refuse coverage.²³ Even when covered, this high price may lead to substantial out-of-pocket burden for patients, potentially impeding the initiation and maintenance of therapy. The result would be less rather than more access to buprenorphine, exactly the

opposite of what federal policy should achieve against the backdrop of a devastating opioid epidemic.

Sublocade's orphan approval was an abuse of orphan drug policy

In my view, Sublocade's orphan approval also represented an abuse of orphan drug policy. Grandfathering an orphan drug designation to a product that would not otherwise qualify for designation did not serve the Orphan Drug Act's purpose to encourage the development of treatments for rare diseases. Moreover, it would be difficult even to argue that grandfathering this designation served a broader societal purpose by prompting Indivior to develop an extended-release buprenorphine injection product in the first place, as at least one competitor (Braeburn Pharmaceuticals) was concurrently developing a similar product despite its inability to receive these incentives.

The campaign to prevent orphan drug exclusivity for Sublocade received widespread support

Braeburn Pharmaceuticals submitted a Citizen Petition to FDA in April 2019

To prevent the possibility of orphan drug exclusivity for Sublocade, thus blocking Brixadi from the market until 2024, Braeburn Pharmaceuticals filed a Citizen Petition in April 2019 calling for the FDA to revoke Sublocade's orphan drug designation and refuse to grant orphan drug exclusivity (or withdraw exclusivity if already granted).¹⁹ This petition garnered substantial support from multiple stakeholders, including patients with opioid use disorder, addiction specialists, and advocacy groups. As of January 2020, of the 51 comments on FDA's website regarding the petition, only two are in opposition, both of which were written by the law firm representing Indivior.¹⁹ The former vice president for public policy of the National

Organization for Rare Disorders (NORD), an advocacy group for patients with rare diseases that benefits from the provisions of the Orphan Drug Act, wrote an editorial arguing that granting exclusivity to Sublocade would constitute an abuse of orphan drug policy with dire consequences for public health.³⁰

Policymakers on both sides of the aisle also voiced opposition to granting orphan drug exclusivity for Sublocade. Former Governor of New Jersey Chris Christie posted a comment on FDA's website supporting the Citizen Petition.¹⁹ Senator Jeanne Shaheen of New Hampshire wrote a letter to Acting FDA Commissioner Norman Sharpless that expressed concerns about the implications of granting orphan drug exclusivity to Sublocade and that requested clarification regarding how FDA tracks sales of orphan drugs approved under cost-recovery prong designations.³¹

FDA revoked orphan drug designation for Subutex in November 2019

On November 7, 2019, FDA ruled in favor of the Citizen Petition, denying Sublocade orphan drug exclusivity.³² Specifically, FDA revoked the 1994 orphan drug designation for Subutex, which meant that this designation could not be grandfathered to Sublocade.

FDA's decision was based on its determination that Reckitt-Benckiser's cost-recovery analysis for Subutex's 1994 application for orphan drug designation was based on unreasonable assumptions. For example, the company assumed that the market size for Subutex would remain constant during the first seven years after approval. In 1994, buprenorphine could only be prescribed at methadone treatment centers, and the company used national data on the number of patients at such centers to estimate the potential number of patients who might take Subutex.³² However, FDA argued that assuming a constant market size was unreasonable due to the high

likelihood of changes in legislation that would allow buprenorphine to be prescribed outside of methadone treatment centers owing to its favorable safety profile. FDA argued that Reckitt-Benckiser itself recognized this likelihood, citing an article authored by the company's vice president that outlined a plan to expand market size through regulatory change.³³ FDA also noted that in its initial review of Reckitt-Benckiser's 1994 cost-recovery analysis, it had conducted nine simulations of cost recovery under different assumptions. In four of these simulations, including a simulation in which market size increased modestly, Subutex would become profitable.³²

FDA also argued that it was unreasonable for the 1994 cost-recovery analysis to only account for sales of Subutex. FDA noted that even in 1994, data suggested that other formulations of buprenorphine could be developed by Reckitt-Benckiser. FDA argued that by failing to account for these other formulations, the cost-recovery analysis may have underestimated potential sales from buprenorphine.³²

Revoking orphan drug designation for Subutex enabled earlier entry of competition to Sublocade

By revoking the orphan drug designation for Subutex and therefore Sublocade, FDA removed one barrier to entry for competitors. The other barrier was a three-year period of exclusivity granted to Sublocade because it was a new formulation of a previously approved drug (i.e., buprenorphine). Braeburn Pharmaceuticals sought to overturn this exclusivity through litigation. A federal judge ruled in favor of Braeburn and ordered FDA to re-examine its decision to grant three-year exclusivity to Sublocade³⁴, but FDA ultimately upheld this exclusivity.³⁵ Consequently, Brixadi and other competing buprenorphine products cannot enter the market until December 1, 2020³⁵, but this is still four years earlier than what would have been allowed had Sublocade been granted orphan drug exclusivity.

H.R. 4712: Fairness in Orphan Drug Exclusivity Act

H.R. 4712 will prevent future exploitation of the loophole that allowed Sublocade's orphan approval

On October 10, 2019, Representative Madeline Dean (D-PA-4) introduced H.R. 4712, the Fairness in Orphan Drug Exclusivity Act.³⁶ H.R. 4712 would amend the Orphan Drug Act in three ways. First, for all future applications for orphan approval under a cost-recovery prong designation, sponsors would have to prove there is no reasonable expectation *at the time of approval* that the lifetime sales of the new drug would be sufficient to recover development and production costs. For example, under current policy, Indivior could theoretically develop a new formulation of buprenorphine-naloxone (Suboxone) and automatically obtain orphan approval under Suboxone's 1994 cost-recovery prong designation, just as it did for Sublocade under Subutex's cost-recovery prong designation. Under H.R. 4712, Indivior would have to prove that the new formulation of Suboxone was unlikely to be profitable, but this would be impossible because Suboxone is a blockbuster drug with billions of sales to date.¹⁹

H.R. 4712 will ensure that Sublocade does not receive exclusivity even if FDA's decision is overturned

Second, for orphan drugs that were approved prior to the enactment of H.R. 4712 under a cost-recovery prong designation, sponsors would have 60 days from enactment to submit a cost-recovery analysis proving that there was no reasonable expectation at the time of approval that the lifetime sales of the drug would be sufficient to recover development and production costs.³⁶ If Indivior successfully sues FDA for revoking Subutex's orphan drug designation, Sublocade would again be entitled to orphan drug exclusivity under current policy. Under H.R. 4712,

however, Indivior would not receive exclusivity unless it could argue that Sublocade was unlikely to be profitable based on data available at the time of approval in November 2017. However, because Indivior has projected Sublocade's peak annual sales to reach \$1 billion¹⁹, it would be unable to make this argument.

H.R. 4712 would allow revocation of orphan approval if drugs become profitable during the exclusivity period

Third, for orphan drugs approved under a cost-recovery prong designation, H.R. 4712 would require sponsors to demonstrate that there is still no reasonable expectation of cost recovery during each of the seven years of orphan drug exclusivity.³⁶ Thus, if such a drug became profitable, orphan approval could be revoked.

H.R. 4712 has a limited scope

An advantage of H.R. 4712 is its limited scope. It would not affect the orphan drug designation process or any orphan approvals under designations granted via prevalence criteria. It would only affect 1) orphan approvals under future designations granted under the cost-recovery prong; 2) Follow-on orphan approvals under the three cost-recovery prong designations that have been granted to date: Subutex (now revoked), Suboxone (which potentially could be revoked by FDA³²), and Eli Lilly's raloxifene (Evista).²⁸

H.R. 4712 is common-sense policy

I strongly support the passage of H.R. 4712. This bill would permanently prevent Indivior from obtaining orphan drug exclusivity for Sublocade, exclusivity that would impede patients' access to life-saving buprenorphine products. H.R. 4712 would also prevent drug companies from exploiting the same loophole that allowed Sublocade to gain orphan approval. In my view,

passing H.R. 4712 is a common-sense step that will be good for orphan drug policy, good for public health, and good for the millions of Americans with opioid use disorder.

Thank you again for the opportunity to participate in today's hearing.

REFERENCES

1. Han B, Compton WM, Blanco C, Jones CM. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults. *Ann Intern Med.* 2018;168(5):383-384.
2. National Center for Health Statistics. *Health, United States, 2017: with Special Feature on Mortality.* Hyattsville, MD, 2018.
3. United Hospital Fund. The Ripple Effect: National and State Estimates of the U.S. Opioid Epidemic's Impact on Children. 2019; https://uhfnyc.org/media/filer_public/6e/80/6e80760f-d579-46a3-998d-1aa816ab06f6/uhf_ripple_effect_national_and_state_estimates_chartbook.pdf. Accessed January 17, 2020.
4. Chua KP, Brummett CM, Conti RM, Bohnert A. Association of Opioid Prescribing Patterns With Prescription Opioid Overdose in Adolescents and Young Adults. *JAMA Pediatr.* 2019.
5. Chua KP, Harbaugh CM, Brummett CM, et al. Association of Perioperative Opioid Prescriptions With Risk of Complications After Tonsillectomy in Children. *JAMA Otolaryngol Head Neck Surg.* 2019.
6. Agarwal S, Bryan JD, Hu HM, et al. Association of State Opioid Duration Limits With Postoperative Opioid Prescribing. *JAMA Netw Open.* 2019;2(12):e1918361.
7. Chua KP, Brummett CM, Waljee JF. Opioid Prescribing Limits for Acute Pain: Potential Problems With Design and Implementation. *JAMA.* 2019.
8. Chua KP, Shrime MG, Conti RM. Effect of FDA Investigation on Opioid Prescribing to Children After Tonsillectomy/Adenoidectomy. *Pediatrics.* 2017;140(6).
9. Chua KP, Conti RM. Out-of-pocket Spending on Orphan Drug Prescriptions Among Commercially Insured Adults in 2014. *J Gen Intern Med.* 2019;34(3):338-340.
10. Chua K, Conti, R. Orphan Drugs For Opioid Use Disorder: An Abuse Of The Orphan Drug Act. 2019; <https://www.healthaffairs.org/doi/10.1377/hblog20190724.795814/full/>. Accessed January 20, 2020.
11. Centers for Disease Control and Prevention. Drug overdose death data. 2018; <https://www.cdc.gov/drugoverdose/data/statedeaths.html>. Accessed September 1, 2018.
12. Florence CS, Zhou C, Luo F, Xu L. The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. *Med Care.* 2016;54(10):901-906.
13. Woolf SH, Schoomaker H. Life Expectancy and Mortality Rates in the United States, 1959-2017. *JAMA.* 2019;322(20):1996-2016.
14. National Safety Council. For the first time on record, your odds of dying from an accidental opioid overdose are greater than dying in a motor-vehicle crash. 2019; <https://injuryfacts.nsc.org/all-injuries/preventable-death-overview/odds-of-dying/>. Accessed January 20, 2020.
15. National Academies of Science E, and Medicine. *Medications for Opioid Use Disorder Save Lives.* Washington, D.C.2019.
16. Kleber HD. Pharmacologic treatments for opioid dependence: detoxification and maintenance options. *Dialogues Clin Neurosci.* 2007;9(4):455-470.
17. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *The Cochrane database of systematic reviews.* 2014(2):CD002207.

18. Barnwal P, Das S, Mondal S, Ramasamy A, Maiti T, Saha A. Probuphine(R) (buprenorphine implant): a promising candidate in opioid dependence. *Ther Adv Psychopharmacol*. 2017;7(3):119-134.
19. Braeburn Inc. Requests that the FDA Revoke Orphan Drug Designation for Sublocade (Buprenorphine Extended-Release) Injection for Treatment of Opiate Addiction in Opiate Users, Currently Referred to as Opioid Use Disorder. 2019; <https://www.regulations.gov/docket?D=FDA-2019-P-1679>. Accessed June 14, 2019.
20. Shover CL, Humphreys K. Predictors of availability of long-acting medication for opioid use disorder. *Drug Alcohol Depend*. 2019;204:107586.
21. Olfson M, Zhang VS, Schoenbaum M, King M. Trends in Buprenorphine Treatment in the United States, 2009-2018. *JAMA*. 2020;323(3):276-277.
22. National Academies of Science, Engineering, and Medicine. *Medications for Opioid Use Disorder Save Lives*. Washington, DC: The National Academies Press, 2019.
23. Kodjak A. In Midst Of Opioid Crisis, FDA May Block New Addiction Drug From Market. 2019; <https://www.npr.org/sections/health-shots/2019/05/24/722076165/in-midst-of-opioid-crisis-fda-may-block-new-addiction-drug-from-market>. Accessed June 14, 2019.
24. Micromedex® (electronic version). <https://www.micromedexsolutions-com>. Accessed January 20, 2020.
25. Bagley N, Berger, M., Chandra, A., Garthwaite, C., Stern, A. The Orphan Drug Act at 30. In: Lerner J, Stern, S., ed. *Innovation Policy and the Economy, 2018, Volume 19 (National Bureau of Economic Research Innovation Policy and the Economy)*. Chicago, IL: University of Chicago Press; 2019.
26. Food and Drug Administration. Orphan Drug Act - Relevant Excerpts. 2018; <https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts>. Accessed January 20, 2020.
27. Lassman S. Orphan drug designation: the gift that keeps on giving. 2019; <https://www.lassmanfdalaw.com/orphan-drug-designation-the-gift-that-keeps-on-giving/>. Accessed January 20, 2020.
28. Karst K. The Rarely Used “Cost Recovery” Path to Orphan Drug Designation and Approval. 2009; <http://www.fdalawblog.net/2009/02/the-rarely-used-cost-recovery-path-to-orphan-drug-designation-and-approval/>. Accessed January 20, 2020.
29. U.S. Congress. H.R.2634 - Drug Addiction Treatment Act of 2000. 2019; <https://www.congress.gov/bill/106th-congress/house-bill/2634>. Accessed January 20, 2020.
30. Dorman D. Don’t let the maker of a buprenorphine drug abuse the Orphan Drug Act. 2019; <https://www.statnews.com/2019/05/28/buprenorphine-drug-abusing-orphan-drug-act/>. Accessed January 20, 2020.
31. Shaheen J. Letter to FDA on Orphan Drug Exclusivity for Monthly Buprenorphine. 2019; <https://www.shaheen.senate.gov/imo/media/doc/2019-09-09-Letter%20to%20FDA%20on%20Orphan%20Drug%20Exclusivity%20for%20Monthly%20Buprenorphine.pdf>. Accessed January 20, 2020.
32. Food and Drug Administration. Response Letter from FDA to Lassman Law + Policy. 2019; <https://www.regulations.gov/document?D=FDA-2019-P-1679-0079>. Accessed January 20, 2020.

33. Jaffe JH, O'Keeffe C. From morphine clinics to buprenorphine: regulating opioid agonist treatment of addiction in the United States. *Drug Alcohol Depend.* 2003;70(2 Suppl):S3-11.
34. United States District Court for the District of Columbia. BRAEBURN INC., Plaintiff, v. UNITED STATES FOOD AND DRUG ADMINISTRATION, et al., Defendants, and INDIVIOR INC., Intervenor-Defendant. 2019; <https://www.bloomberglaw.com/public/desktop/document/BraeburnIncvFDANo19982BAH2019BL269438DDCJuly222019CourtOpinion?1579547547>. Accessed January 20, 2020.
35. Braeburn Pharmaceuticals. FDA Grants Braeburn's Citizen Petition Allowing BRIXADI (buprenorphine) Extended-Release Injection for Opioid Use Disorder to be Available in December 2020. 2019; <https://braeburnrx.com/fda-grants-braeburns-citizen-petition-allowing-brixadi-buprenorphine-extended-release-injection-for-opioid-use-disorder-to-be-available-in-december-2020/>. Accessed January 20, 2020.
36. U.S. Congress. H.R.4712 - Fairness in Orphan Drug Exclusivity Act. 2019; <https://www.congress.gov/bill/116th-congress/house-bill/4712>. Accessed January 20, 2020.

Supporting document: *Health Affairs* blog post

Publication date: 7/26/19

Link: <https://www.healthaffairs.org/doi/10.1377/hblog20190724.795814/full/>

Title: Orphan Drugs for Opioid Use Disorder: An Abuse of the Orphan Drug Act

Authors: Kao-Ping Chua, Rena M. Conti

In November 2017, the drug company Indivior received Food and Drug Administration (FDA) approval for Sublocade, a once-monthly buprenorphine injection for patients with opioid use disorder. In December 2018, Braeburn Inc. received FDA approval for a similar product but could not sell it due to Indivior's marketing exclusivity period. Typically, the FDA grants three years of marketing exclusivity for new formulations of previously approved drug such as buprenorphine. However, in a controversial decision, the FDA approved Sublocade under a 1994 orphan designation for one of the company's prior buprenorphine products. Consequently, under the Orphan Drug Act of 1983, Sublocade is entitled to a seven-year period of marketing exclusivity (so-called orphan drug exclusivity).

Despite this entitlement, it is currently unclear whether the FDA has granted orphan drug exclusivity. To prevent this possibility, Braeburn Inc. filed a Citizen Petition in April 2019, calling for the FDA to revoke Sublocade's orphan designation and refuse to grant orphan drug exclusivity (or withdraw exclusivity if already granted). This petition—which is separate from a lawsuit that Braeburn Inc. filed to overturn a three-year marketing exclusivity period for Sublocade—argues that Sublocade is not a bona fide orphan drug because opioid use disorder, a disease that affects more than two million Americans, is not a rare orphan disease.

As of the time of writing, the FDA has not decided on the petition. By statute, the agency has 150 days to respond. We will provide policy context for this controversy and argue that the FDA should not allow orphan drug exclusivity for Sublocade.

Allowing Orphan Drug Exclusivity Could Worsen Access to Treatment For Opioid Use Disorder

Medications for opioid use disorder include methadone, buprenorphine, and extended-release naltrexone. Although these medications can be life-saving, many patients with opioid use disorder do not receive them in a timely fashion, in part because access is impeded by barriers such as stigma, insufficient clinician education, and refusal by some insurers to cover the medications.

If Sublocade receives orphan drug exclusivity, access could be further impeded. All products for opioid use disorder that contain buprenorphine would be barred from market entry until December 2024, even if they are not extended-release injections. The resulting monopoly would not only stifle innovation but would also allow Indivior an extended period during which it could charge high prices. The list price for each monthly dose of Sublocade is currently \$1,580, prompting some payers to refuse to cover the drug. Even when covered, this high price may lead to substantial out-of-pocket burden for patients, potentially impeding the initiation and maintenance of therapy. Against the backdrop of an opioid epidemic claiming the lives of 47,000 Americans per year, federal policy should expand rather than limit access to medications for opioid use disorder.

The Original Orphan Designation Was Made On Questionable Grounds

Congress passed the Orphan Drug Act in 1983 to encourage the development of drugs for rare diseases, which historically had few therapeutic options due to the small markets for such drugs. Incentives under the act include tax credits and grants for clinical testing, a waiver of FDA user fees for drug applications, and orphan drug exclusivity. To receive these incentives, companies must first obtain orphan designation for a drug, after which they must receive FDA approval for a specific orphan indication. In the original act, designation was granted if there was no “reasonable expectation” that sales would be sufficient to recoup the costs of development and marketing. The following year, the act was amended so that designation could also be granted if the targeted disease affected 200,000 Americans or fewer.

Since 1983, all but three orphan drugs have been designated based on prevalence criteria. Two of these three drugs were buprenorphine tablets (Subutex) and buprenorphine/naloxone tablets (Suboxone), both of which were designated in 1994 for opioid use disorder. Reckitt Benckiser Pharmaceuticals, the drugs’ manufacturer and parent company of Indivior, could not obtain these orphan designations via prevalence criteria because opioid use disorder was not a rare disease in 1994, just as it is not today. Rather, Reckitt Benckiser argued that the drugs would not be economically viable, citing sales projections that assumed buprenorphine would only be prescribed in the small number of treatment centers that dispensed methadone.

In 2000, the Drug Addiction Treatment Act—legislation for which Reckitt Benckiser aggressively lobbied—allowed buprenorphine prescribing in office-based settings. Both Subutex and Suboxone were approved in 2002 and received orphan drug exclusivity. Between 2002 and 2011, Subutex generated \$285 million in sales while Suboxone’s sales reached billions of dollars, figures that controverted the notion that these drugs had limited economic potential.

Allowing Orphan Drug Exclusivity Would Not Serve the Purpose of The Orphan Drug Act

In 2017, the FDA approved Sublocade under the 1994 orphan designation for Subutex because both drugs contained the same active moiety and were made by the same company (Indivior spun off from Reckitt Benckiser in 2014). Thus, Sublocade became the company's third orphan drug for opioid use disorder, even though it did not treat a rare disease and even though the economic viability of buprenorphine products had been demonstrated. Indivior itself predicts that Sublocade will reach \$1 billion in peak annual sales, thus negating the possibility that the company could have obtained a new orphan designation for Sublocade based on the Orphan Drug Act's economic viability criteria.

Grandfathering an orphan designation to a product that would not otherwise qualify for designation does not serve the Orphan Drug Act's purpose to encourage the development of treatments for rare diseases. Moreover, it would be difficult even to argue that grandfathering this designation served a broader societal purpose by prompting Indivior to develop an extended-release buprenorphine injection product in the first place since at least one competitor (Braeburn Inc.) was concurrently developing a similar product despite its inability to receive these incentives.

Conclusion

Regardless of how the FDA rules on this particular case, we believe it should prevent future similar controversies by prohibiting grandfathering of orphan designations going forward. Rather, the FDA should require that criteria for orphan designation are still met each time a drug is approved under a previously granted designation. Additionally, when evaluating future applications for orphan designation based on economic viability, the FDA should require

independent sales projections from entities without a vested interest in the outcome of the application.

We hope, however, that the FDA does not allow orphan drug exclusivity for Sublocade, based on the serious public health ramifications of limiting access to treatments for opioid use disorder, the questionable grounds on which the original orphan designation was approved, and the disconnect between allowing exclusivity and the purpose of the Orphan Drug Act. Ruling otherwise would needlessly jeopardize the health of millions of Americans with opioid use disorder.