December 26, 2024

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Re: Docket No. FDA-2022-P-1863

Dear Dr. Coyle:

This letter responds to your citizen petition received by the Food and Drug Administration (FDA or Agency) on January 27, 2023 (FDA-2022-P-1863) (Petition) and submitted by the Colorado Society of Addiction Medicine. The Petition requests the following:

1) Update language in the labeling of sublingual buprenorphine products[1] approved to treat opioid use disorder (OUD). This [petition] requests that labeling include the following statement:

   Following initiation, buprenorphine dose should be titrated based on the prescriber's clinical judgment to alleviate symptoms enough to enable patients to maintain discontinuation of illicit opioid use. Evidence suggests that 16 [milligrams (mg)] per day or more may reduce risk of overdose death more effectively than lower doses. Some patients may require a higher than average dose due to significant inter-patient variability in opioid tolerance, drug absorption, and drug metabolism such as during pregnancy.

2) Issue a drug safety communication (DSC) to providers highlighting the potential clinical benefit of sublingual buprenorphine doses ≥16mg/day in patients with OUD.[2]

We have carefully considered your Petition and other available information, and for the reasons stated below, the Petition is granted in part and denied in part.

I. BACKGROUND

A. Buprenorphine

Buprenorphine is a partial agonist at the mu-opioid receptors, an antagonist at kappa and delta

[1] Although the Petition specifically addresses sublingual buprenorphine products indicated for the treatment of opioid use disorder, this response will address buprenorphine-containing transmucosal products for the treatment of opioid dependence (BTODs) more broadly (rather than just sublingual products) as the language in the labeling identified in the Petition is common to all BTODs.
[2] Petition at 1.

opioid receptors, and an agonist at the nociception opioid-receptor-like-1 (ORL-1) receptors.[3] Buprenorphine produces typical mu-opioid agonist effects including analgesia, euphoria, sedation, respiratory depression, and pupillary constriction. However, as a partial agonist, buprenorphine may also behave as an antagonist depending on the state of the activation of the opioid receptor system, partially blocking the effects of full agonists. The ability of buprenorphine to attenuate or block the effects of full opioid agonists is a desirable effect that helps to underlie its use as pharmacotherapy for treatment of opioid use disorder.[4] Because buprenorphine is subject to misuse, abuse, and diversion, it is controlled under schedule III of the Controlled Substances Act (CSA).[5]

Buprenorphine was first marketed in 1981 as an injectable analgesic.[6] Presently, buprenorphine is available in various dosage forms (i.e., sublingual and buccal film, sublingual tablet, transdermal film, intravenous/subcutaneous injection) and is indicated for the management of pain[7] or for the treatment of opioid use disorder.[8]

Buprenorphine products indicated for the treatment of opioid use disorder are available both as products containing buprenorphine alone and in fixed combination containing buprenorphine with naloxone. All buprenorphine-containing transmucosal products (i.e., those where the dose of the drug is delivered across mucous membranes, such as inside the cheek or under the tongue) for the treatment of opioid dependence (BTODs)[9] contain language in the labeling similar to the language in the current Suboxone labeling:[10]

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[3] Lewis, JW, 1985, Buprenorphine, Drug Alcohol Depend, 14(3-4): 363-372; Lewis, JW and SM Husbands, 2004, The orvinols and related opioids--high affinity ligands with diverse efficacy profiles, Curr Pharm Des, 10(7): 717-732; Lutfy, K and A Cowan, 2004, Buprenorphine: a unique drug with complex pharmacology, Curr Neuropharmacol, 2(4): 395-402.

[4] Mello, NK and JH Mendelson, 1980, Buprenorphine suppresses heroin use by heroin addicts, Science, 207(4431): 657-659; Strain, EC, ML Stitzer, IA Liebson, and GE Begelow, 1994, Comparison of buprenorphine and methadone in the treatment of opioid dependence, Am J Psychiatry, 151(7): 1025-1030; Walsh, SL, KL Preston, GE Bigelow, and ML Stitlzer, 1995, Acute administration of buprenorphine in humans: partial agonist and blockade effects, J Pharmacol Exp Ther, 274(1): 361-372; Walsh, SL, KL Preston, ML Stitzer, EJ Cone, and GE Bigelow, 1994, Clinical pharmacology of buprenorphine: ceiling effects at high doses, Clin Pharmacol Ther, 55(5): 569-580; Johnson, RE, JH Jaffe, and PJ Fudala, 1992, A controlled trial of buprenorphine treatment for opioid dependence, JAMA, 267(20): 2750-2755.

[5] 21 CFR 1308.13(e)(2).

[6] Information about Buprenex (buprenorphine hydrochloride (HCl)) injection, the first FDA-approved buprenorphine product, is available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm by searching under the name, "Buprenex."

[7] See, e.g., labeling for Belbuca (buprenorphine HCl) buccal film (December 15, 2023), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207932s019s020lbl.pdf.

[8] See, e.g., labeling for Suboxone (buprenorphine HCl and naloxone HCl) sublingual film (December 15, 2023), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/022410s052lbl.pdf; labeling for Sublocade (buprenorphine HCl extended-release) injection (December 15, 2023), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209819Orig1s026lbl.pdf.

[9] BTODs include Zubsolv (buprenorphine HCl and naloxone HCl) sublingual tablets, Suboxone (buprenorphine HCl and naloxone HCl) sublingual film, buprenorphine HCl and naloxone HCl sublingual film, buprenorphine HCl and naloxone HCl sublingual tablets, and buprenorphine HCl sublingual tablets.

[10] Labeling for Suboxone (buprenorphine HCl and naloxone HCl) sublingual film (December 15, 2023). The dosages of buprenorphine described in this response (e.g., 16 mg/day, 24 mg/day) are based on the bioavailability of

> After treatment induction and stabilization, the maintenance dose of SUBOXONE sublingual film is generally in the range of 4 mg/1 mg buprenorphine/naloxone to 24 mg/6 mg buprenorphine/naloxone per day depending on the individual patient and clinical response. The recommended target dosage of SUBOXONE sublingual film during maintenance is 16 mg/4 mg buprenorphine/naloxone/day as a single daily dose. Dosages higher than 24 mg/6 mg daily have not been demonstrated to provide a clinical advantage.

B. Statutory and Regulatory Standard for Updating Labeling

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), applicants seeking to market a new drug generally must first submit an application to FDA for approval. The FD&C Act makes it unlawful to market a new drug product without first obtaining an approved new drug application (NDA) or abbreviated new drug application (ANDA).[11] A supplement to an NDA is generally required for a change to the information required in labeling, including changes to the Dosage and Administration section, with certain exceptions.[12] For some labeling changes, FDA cannot approve the supplement unless there is adequate evidence demonstrating the safety and effectiveness of the drug for the conditions of use reflected in the proposed change.[13]

For most substantive changes to the labeling for drug products, including changes to the Dosage and Administration section, the application holder is required to seek and obtain FDA approval for the change.[14] Only the holder of an approved application may submit a supplement to an application.[15]

C. Drug Safety Communication

A Drug Safety Communication (DSC) is one tool for communicating important new and emerging safety information to the public. After a drug is approved, FDA maintains a system of postmarketing surveillance and risk assessment programs to identify adverse events that did not appear during the drug approval process. When FDA becomes aware of a potential new safety issue, the Agency will review data from available clinical trials or other studies, case reports, and medical literature. Based on the Agency's review, FDA may take regulatory action, including updating a product's labeling information, sending out a "Dear Healthcare Professional" letter, or, in rare cases, removing a product from the market. The Agency may also issue a DSC to alert patients and healthcare professionals to new safety issues. DSCs can highlight such issues when they pose potentially serious or life-threatening risks or adverse events. DSCs can also be used

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Suboxone sublingual tablets. Some buprenorphine/naloxone products may provide equivalent buprenorphine exposure at alternate dosages due to differences in formulation.

[11] See section 505(a) of the FD&C Act (21 U.S.C. 355(a)); see also section 301(d) of the FD&C Act (21 U.S.C. 331(d)) (prohibiting the marketing of any article in violation of section 505).

[12] 21 CFR 314.70(b)(2)(v)(C).

[13] FD&C Act 505(d). See also Otsuka Pharm. Co. v. Burwell, No. GJH-15-852, 2015 WL 3442013, at *1 (D. Md. May 27, 2015) (Noting that "FDA will refuse to approved the [supplemental NDA] if, among other reasons, the sponsor's investigations do not show that the drug is safe or effective for the 'the conditions of use prescribed, recommended, or suggested in the proposed labeling.'").

[14] See 21 CFR 314.70(b).

[15] See 21 CFR 314.70(a).

to communicate information about a previously unknown drug interaction, a potential medication error such as drug name confusion that may result in a serious or life-threatening adverse reaction, or even updated information about a known adverse event.

II. DISCUSSION

The Petition raises concerns about the rise in fentanyl and other synthetic opioids contributing to the opioid epidemic.[16] The Petition further states that "[a]djusting the recommended dosing limits…is one action the FDA can take that can help improve outcomes for patients and providers fighting in the opioid epidemic."[17] We share the Petition's concerns about the role fentanyl and its analogs may play in contributing to the opioid crisis. We also agree that wider access to buprenorphine as treatment for OUD is needed.

In light of the important role buprenorphine can play as a treatment option for OUD, FDA is committed to doing its part to lower access barriers for buprenorphine products as one strategy to help address the current opioid crisis. Over the last several years, FDA has taken a number of steps to improve availability of buprenorphine products while ensuring their safety and effectiveness. For example, on March 20, 2024, the BTOD risk evaluation and mitigation strategy (REMS) was modified, in part, to update the prescriber and pharmacist educational materials to be consistent with the full prescribing information regarding buprenorphine dosing, naloxone use, and counseling and psychosocial support.[18] On May 23, 2023, FDA approved Brixadi (buprenorphine) extended-release injection to treat moderate to severe OUD. Because Brixadi is available in two formulations, a weekly injection and a monthly injection, this approval expands dosing options. On May 9, 2023, we also issued a joint letter with the Substance Abuse and Mental Health Services Administration (SAMHSA) to clarify the importance of counseling and other services as part of a comprehensive treatment plan for OUD, and to also reiterate that providing buprenorphine should not be made contingent upon participation in such services.[19] We have also issued guidance to help facilitate the development of treatments for OUD, including buprenorphine products.[20] Lastly, FDA participated in several meetings, including a two-day public meeting with the Reagan-Udall Foundation for the FDA in May 2023 and two listening sessions led by SAMHSA in November and December 2023 to understand dosing of buprenorphine.[21]

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[16] Petition at 4.
[17] Petition at 4.
[18] Update to Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS (March 2024), available at https://www.accessdata.fda.gov/drugsatfda_docs/rems/BTOD_2024_03_20_REMS_Full.pdf.
[19] Letter from SAMHSA and FDA (May 9, 2023), available at https://www.samhsa.gov/sites/default/files/dear-colleague-letter-fda-samhsa.pdf.
[20] See guidance for industry, Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Treatment (October 2020); guidance for industry, Opioid Use Disorder: Developing Depot Buprenorphine Products for Treatment (February 2019). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[21] See Considerations for Buprenorphine Initiation and Maintenance Care (May10-11, 2023), available at https://reaganudall.org/news-and-events/events/considerations-buprenorphine-initiation-and-maintenance-care; Meeting Summary, Listening Session: Use of High Dose Buprenorphine for the Treatment of Opioid Use Disorder; (December 11, 2023), available at https://store.samhsa.gov/sites/default/files/high-dose-buprenorphine-report-pep24-02-013.pdf; Tribal Listening Session: Use of High Dose Buprenorphine for the Treatment of Opioid Use

As discussed above, the Petition requests that FDA take certain actions with respect to BTODs. For the reasons set forth below, the Petition is granted to the extent that the Agency has taken affirmative steps to facilitate changes to BTOD labeling to clarify recommendations regarding, maintenance doses of buprenorphine (i.e., 16 mg/day "target dose" and statement that "[d]osages higher than 24 mg/6 mg daily have not been demonstrated to provide a clinical advantage"). The Petition is denied to the extent that FDA has concluded that the specific labeling language requested in the Petition lacks adequate scientific support, and that FDA cannot unilaterally update the approved labeling of drug products. The Petition is further granted to the extent that FDA is today issuing a communication to stakeholders, including healthcare practitioners, to emphasize that BTOD labeling does not include a maximum dosage. The Petition is denied to the extent that it requests FDA to use a DSC as the vehicle for that communication.

A. The Petition's Requested Labeling

The Petition states that the current labeling for BTODs "is inadequate to meet the needs of the American population during a synthetic opioid overdose epidemic."[22] Accordingly, the Petition requests that FDA revise BTOD labeling as follows:

> *Following initiation, buprenorphine dose should be titrated based on the prescriber's clinical judgment to alleviate symptoms enough to enable patients to maintain discontinuation of illicit opioid use. Evidence suggests that 16mg per day or more may reduce risk of overdose death more effectively than lower doses. Some patients may require a higher than average dose due to significant inter-patient variability in opioid tolerance, drug absorption, and drug metabolism such as during pregnancy.*[23]

To evaluate the Petition's request, we reviewed the literature and other information cited in the Petition and also conducted our own literature review. Based on our review and analysis of available literature and information, it is FDA's view that the data and information do not support the specific labeling revisions proposed in the Petition.

However, we recognize that the labeling for BTODs may be misinterpreted by some as establishing a maximum dosage when none exists, and we are concerned that misinterpretation of the labeling may be adversely impacting patients' access to BTODs. Accordingly, today we are issuing a *Federal Register* notice titled, Modifications to Labeling Buprenorphine-Containing Transmucosal Products for the Treatment of Opioid Dependence to encourage the submission of supplemental NDAs to modify the labeling for BTODs. In the notice, we recommend revisions to maintenance dosage recommendations in the "Dosage and Administration" section and the "Pregnancy" subsection of the "Use in Specific Populations" section of BTOD labeling to make clear that there are no maximum dosage limits and that certain populations, including pregnant

Disorder (November 13, 2023), available at SAMHSA's Office of Tribal Affairs and Policy website, https://www.samhsa.gov/tribal-affairs/news-events.

[22] Petition at 2.

[23] Petition at 1.

females,[24] may require a higher buprenorphine dosage. Thus, the Petition is granted to the extent the Agency has taken affirmative steps to facilitate changes to BTOD labeling to clarify recommendations regarding maintenance doses of buprenorphine.

1. Review of Petition's Cited Studies

Our consideration of the Petition's recommended labeling language focuses on the removal of the statement, "Dosages higher than 24 mg/6 mg daily have not been demonstrated to provide a clinical advantage" in current BTOD labeling and the inclusion of the Petition's requested statement, "Evidence suggests that 16mg per day or more may reduce risk of overdose death more effectively than lower doses." The Petition's other recommended labeling statements, "Following initiation, buprenorphine dose should be titrated based on the prescriber's clinical judgment to alleviate symptoms enough to enable patients to maintain discontinuation of illicit opioid use" and "Some patients may require a higher than average dose due to significant inter-patient variability in opioid tolerance, drug absorption, and drug metabolism such as during pregnancy" are concepts already captured in current BTOD labeling. For example, current Suboxone labeling already recommends that buprenorphine/naloxone dosages from day 3 onwards should be "progressively adjusted in increments/decrements of 2 mg/0.5 mg or 4 mg/1mg buprenorphine/naloxone to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms."[25] Further, the labeling recognizes inter-patient variability as current BTOD labeling notes that the maintenance dosages are "generally in the range of 4 mg/1 mg buprenorphine/naloxone to 24 mg/6 mg buprenorphine/naloxone per day depending on the individual patient and clinical response."[26]

The Petition states that the current BTOD labeling, which includes the statement, "dosages higher than 24 mg/6 mg daily have not been demonstrated to provide a clinical advantage," "does not reflect the current literature[,] which supports the potential for improved outcomes for patients with OUD with daily buprenorphine doses greater than 24mg."[27] The Petition's proposal notably omits the statement, "dosages higher than 24 mg/6 mg daily have not been demonstrated to provide a clinical advantage," from its recommended labeling language. The Petition goes on to cite several studies to support the position that there is "the potential for improved outcomes for patients with OUD with daily buprenorphine doses greater than 24mg." The Petition recognizes that the data from these studies "are predominantly observational, and that no high-quality clinical trials evaluating outcomes between dosing groups exist to support or refute" the Petition's requested actions.[28]

[24] The term female or male is used in the classification of sex, according to their reproductive organs and functions assigned by chromosomal complement. FDA recognizes that sex and gender are distinct terms, with sex defined as a biological construct and gender as a social construct. For more information, see guidance for industry, Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs (November 2020).

[25] Labeling for Suboxone (buprenorphine HCl and naloxone HCl) sublingual film (December 15, 2023).

[26] Id.

[27] Petition at 3.

[28] Petition at 4. The Petition further claims that "FDA has taken labeling and/or regulatory action on spontaneous case reports – so there is a precedent for changing labeling in the setting of imperfect data" (id.). The Petition does not identify what specific actions the Agency has taken. However, "spontaneous case reports" are associated with safety concerns, and the standards for requiring safety labeling changes based on new safety information are set

Further, the Petition requests that the labeling be updated, in part, to include the statement, "Evidence suggests that 16mg per day or more may reduce the risk of overdose death more effectively than lower doses."[29] The studies cited in the Petition do not support inclusion of this statement in BTOD labeling. None provides direct evidence evaluating the relationship between buprenorphine dose and mortality. Although these studies may indicate an association between OUD treatment retention and/or measures of opioid use and higher doses of buprenorphine, many factors, aside from buprenorphine dose have the potential to reduce mortality risk, including provider effects (e.g., variation in clinical practice), concurrent non-pharmacologic treatment, socioeconomic factors, and support from additional sources, such as social work, family, friends, and self-help groups.

As explained further below, the studies referenced in the Petition do not support the Petition's request to update labeling with the Petition's recommended labeling language.

The Petition cites to a 2014 study by Hser et al. and claims that it "showed a linear relationship between medication dose and retention for patients receiving buprenorphine, with no reported serious adverse medication-related outcomes among patients receiving doses >24mg/day."[30] The study authors conducted secondary analyses of data from a clinical trial that occurred at nine opioid treatment programs across the United States from 2006 through 2009.[31] There were 1,267 participants included in the analyses, with 738 receiving buprenorphine and 529 receiving methadone.[32] The study evaluated treatment completion (i.e., continuing the assigned medication for the full 24 weeks) and retention (i.e., number of days in treatment) by daily dose.[33] The study grouped subjects into five categories with study subjects receiving the following maximum buprenorphine daily dose in the 24-week trial: 0-10, 12-14, 16-20, 22-28, 30-32 mg/day.[34]

Based on our review of the study, we cannot conclude that there is a linear relationship between medication dose and retention for patients. The study authors note that there was a linear trend between percent of study completion and the maximum dose of buprenorphine, with those receiving 30-32 mg/day (27.6 percent of participants) having a completion rate of about 60 percent.[35] However, the study does not describe the results of any formal analysis to test for linearity across the five dose groups, nor is there a statistical comparison of between-group

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forth in the statute. See section 505-1(b)(3) of the FD&C Act, which states that the term "new safety information" means "information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3)), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of this title; or other scientific data deemed appropriate by [FDA]....."

[29] Petition at 1.

[30] Petition at 3 citing to Hser, YI, AJ Saxon, D Huang, A Hasson, C Thomas, M Hillhouse, P Jacobs, C Teruya, P McLaughlin, K Wiest, A Cohen, and W Ling, 2014, Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial, Addiction, 109(1):79-87, doi: 10.1111/add.12333, Epub 2013 Oct 9. PMID: 23961726; PMCID: PMC3947022.

[31] Primary analyses were previously published and assessed liver health outcomes over 24 weeks following randomization of patients into buprenorphine or methadone treatment. Hser et al. at 80.

[32] Id. Two women who became pregnant were excluded from the study group, resulting in 1,267 participants.

[33] Id.

[34] Id. at 81.

[35] Id.

differences or adjustment for potential confounders in the comparison across the five dose groups in this analysis. Moreover, the most impactful gains in retention appear to be associated with the change in dose from the 0-10 mg/day to the 12-14 mg/day category or from the 12-14 mg/day to the 16-20 mg/day category, with smaller numerical gains in retention between the 22-28 mg/day and 30-32 mg/day categories.[36] Importantly, it is unclear from the data whether these differences were statistically significant. Of note, separate adjusted analyses were also conducted using buprenorphine dose on the last day of treatment, which showed that ≥16 mg/day was significantly associated with lower risk of dropout compared to lower daily dose (<16 mg). Additionally, ≥16 mg/day was slightly negatively associated with continued opioid use, particularly in the first nine weeks of treatment.

The high number of participant dropouts also raises concerns about the conclusions reached in the study. Buprenorphine patients had a lower percentage of treatment completion (46 percent) and mean number of days in treatment (103.8 days) compared to methadone (74 percent and 141.3 days).[37] The study noted that more buprenorphine participants (25.6 percent) than methadone participants (12.4 percent) dropped out because they no longer wished to participate.[38] Study subjects were not blinded to their buprenorphine dose, which may have influenced their reason for dropping out. The results of this study also raise the possibility of reverse causation, whereby the association of longer retention among patients at higher doses could be explained, at least partially, by longer time in treatment, which increases the chance of reaching higher doses with those remaining in the study until the end of the 24-week trial having the greatest opportunity to be exposed to higher doses at some point during their treatment.

Finally, patients were randomized to buprenorphine and methadone assignment, not buprenorphine dose. Therefore, any associations identified between buprenorphine dose and retention are subject to potential confounding factors and other limitations of an observational study, such as channeling bias, which can occur when a healthcare practitioner chooses a dose for each specific patient based on different prognostic characteristics.

Based on our review of the Hser et al. study, we have determined that a linear relationship between medication dose and retention for patients has not been conclusively established. Notably the study authors state the "possibility of [buprenorphine] at a dose of 32 mg or higher having a potential impact on improving treatment retention and outcome" but "further investigations of the safety, efficacy and clinical utilities of higher doses of [buprenorphine] should be considered."[39] Regarding the Petition's statement on the clinical benefit of ≥16 mg/day, this study provides some support that patients taking ≥16 mg/day may have longer retention compared to patients taking <16 mg/day.

The Petition states that a study authored by Pizzicato et al. "showed that doses >24 mg/day were associated with significantly greater 180-day buprenorphine adherence when compared to doses

[36] See id. at 83, Figure 1.
[37] Id. at 81.
[38] Id.
[39] Id. at 85.

<16 mg/day."[40] The study authors conducted a retrospective cohort study using data from Pennsylvania's Prescription Drug Monitoring Program for 2017 and 2018. This study focused on Philadelphia residents initiating buprenorphine, defined as not having received a buprenorphine dispensing in the 180 days prior.[41] The main outcome of the study was medication adherence, defined as ≥80 percent of days covered by a buprenorphine dispensing over the 180-day follow-up period.[42] The total sample size was 10,669.[43] Overall, 26.6 percent of patients were adherent at 180 days, with patients on "medium" (16 to <24 mg) and "high" (≥24 mg) daily dose having higher odds of being adherent than those with "low" (<16 mg) daily dose prescriptions.[44]

Based on our review of the study, we do not agree with the Petition that the Pizzicato et al. study "showed that doses >24 mg/day were associated with significantly greater 180-day buprenorphine adherence when compared to doses <16 mg/day."[45] Nearly all (96.7 percent) patients in the "high" dose category were prescribed exactly 24 mg/day of buprenorphine, with only 24 patients on >24 mg/day. Further, the study did not report any test for statistical significance with respect to the 24 patients on >24 mg/day of buprenorphine. Notably, 24 mg/day is within the range of effective maintenance doses (i.e., 4 mg–24 mg or equivalent) as described in current BTOD labeling. While the study by Pizzicato et al. suggests that doses ≥24 mg/day could be beneficial for adherence, this study does not provide evidence for a clinical advantage of >24 mg/day compared to 24 mg/day, or to lower daily doses.[46] Additionally, results from this study were subject to many of the limitations identified for this body of evidence and described in section II.A.2.ii of this letter.

The Petition further cites to a study authored by Fareed et al. to support the claim that "patients receiving buprenorphine dosages from 16-32 mg/day showed better retention in treatment than groups receiving <16 mg/day, with fewer urine tests positive for opiates and cocaine."[47] The study authors conducted a literature search described as a "meta-analysis" to compare outcomes among patients using daily buprenorphine doses of ≥16 mg/day to <16 mg/day.[48] The authors identified 21 clinical trials that met certain inclusion criteria and were published between 1960

[40] Petition at 3 citing to Pizzicato, LN, JK Hom, M Sun, CC Johnson, and KM Viner, 2020, Adherence to buprenorphine: An analysis of prescription drug monitoring program data, Drug Alcohol Depend, 216:108317, doi: 10.1016/j.drugalcdep.2020.108317, Epub 2020 Sep 28. PMID: 33035714.
[41] Pizzicato et al. at 2.
[42] Id.
[43] Id.
[44] Id.
[45] Petition at 3.
[46] We note that the study had several limitations including that the PDMP data cannot be generalizable as they were limited to only Philadelphia residents and do not capture prescriptions dispensed from opioid treatment programs, hospitals and correctional facilities or filled out of state. Additionally, patients who switched to methadone from buprenorphine would be counted as not adherent even though they continued treatment. Further, adherence was measured by the days' supply of buprenorphine rather than actual use. Finally, overlapping prescriptions were appended to the total days' supply, and thus, patients may have received multiple prescriptions if their dose was adjusted, further complicating assignment to buprenorphine dose groups.
[47] Petition at 3 citing to Fareed, A, S Vayalapalli, J Casarella, and K Drexler, 2012, Effect of buprenorphine dose on treatment outcome, J Addict Dis, 31(1):8-18, doi: 10.1080/10550887.2011.642758. PMID: 22356665.
[48] Fareed et al. at 9.

and 2010.[49] A total of 2,703 participants were included in the study.[50] The study authors concluded that "[t]here is strong evidence based on 21 randomized clinical trials that the higher buprenorphine dose may improve retention in buprenorphine maintenance treatment."[51]

The study suffers from significant design flaws that render the study results uninterpretable. For example, to be included in the analysis, a trial had to be "[r]andomized, controlled, or double-blind clinical trials with buprenorphine as the study drug," but the studies only needed to satisfy one of these conditions, not all three.[52] Further, as acknowledged by the study authors, the identified studies are heterogeneous in terms of study population (e.g., youth, persons with HIV, persons with heroin-dependence, U.S. and non-U.S. studies) and interventions, which the authors do not appear to evaluate or include as a consideration in their analytic approach. Most of the included trials randomized patients to buprenorphine for maintenance versus another treatment modality, such as methadone, short term buprenorphine use for detoxification, or referral to a treatment program. In these trials, participants randomized to buprenorphine are dosed on a flexible dosing schedule based on clinician judgment. The study authors then use either the mean or maximum doses reported for a buprenorphine flexible dosing arm to further segregate the studies into two categories: buprenorphine ≥16 mg or buprenorphine <16 mg. Therefore, treatment arms from different studies are pooled together and then compared, ignoring the randomization scheme of the original clinical trial. In conducting a trial-level (not patient-level) secondary analysis across multiple trials that do not share the same primary objective, and including trials in which patients were not randomized to buprenorphine dose, this study failed to account for either trial-level or individual-level confounding. Further, there is no differentiation between different buprenorphine formulations (e.g., buprenorphine sublingual solution and buprenorphine sublingual tablet), which may result in different exposure levels.

The Petition cites to two studies by the same primary author, Greenwald. For the first study, the Petition states it "showed that sublingual buprenorphine dose-dependently increased mu opioid receptor occupancy, with near-maximal receptor occupancy levels occurring at doses of 32 mg/day (89-99 percent occupancy relative to placebo)."[53] The Petition further asserts that the study "demonstrated that high buprenorphine occupancy of mu receptors correlated with decreased withdrawal and reward symptoms, with near-maximal effects observed at doses of 32 mg/day."[54] For the second study, the Petition notes that "the same author concluded that buprenorphine doses of 16mg/day may be adequate to achieve clinically meaningful opioid blockage in some patients; however, achieving blockage of the subjective effects of high opioid doses in most patients may require buprenorphine doses greater than 24 to 32mg/day."[55] We

[49] Id. at 11.
[50] Id.
[51] Id. at 15.
[52] Id. at 10.
[53] Petition at 3 citing to Greenwald, MK, CE Johanson, DE Moody, JH Woods, MR Kilbourn, RA Koeppe, CR Schuster, and JK Zubieta, 2003, Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers, Neuropsychopharmacology, 28(11):2000-2009, doi:10.1038/sj.npp.1300251.
[54] Id.
[55] Petition at 3-4 citing Greenwald, MK, SD Comer, and DA Fiellin, Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy, Drug Alcohol Depend, 144:1-11. doi:10.1016/j.drugalcdep.2014.07.035.

agree that studies evaluating plasma buprenorphine concentration, receptor occupancy, and pharmacodynamic effects (e.g., drug liking, opioid blockade), such as the two studies cited in the Petition, suggest buprenorphine plasma concentrations of at least 2-3 ng/ml may be required for full opioid blockade. However, these are intermediate endpoints, which may be helpful in predicting clinical benefit, but are not adequate to support the Petition's requested labeling change.

The Petition further references a study of hospitalized men with OUD claiming that it "showed a single high dose (32 mg, 64 mg, 96 mg) of sublingual buprenorphine reduced cravings in a dose-response manner over the next 5 days, with no serious adverse cardiovascular or respiratory events observed."[56] Although the study demonstrated lower visual analog scale craving for both the 64 mg and 96 mg dosage groups versus the 32 mg dosage group, two participants in the 96 mg dosage group experienced hypotension requiring treatment with hydration, and two participants in the 64 mg dosage group and three participants in the 96 mg dosage group experienced nausea and vomiting resulting in treatment with anti-emetic medication.[57] Further, the study provides little insight into the Petition's position that dosages greater than 24 mg have a clinical advantage over doses less than 24 mg (or less than 16 mg) because the study does not make this comparison. Nor does the study include endpoints that are relevant to the Petition's request, such as mortality, treatment retention or patterns of opioid use. We also determined that the study results have limited generalizability because it involved only male inpatients in Iran.

The Petition contends that "[m]ultiple trials of sublingual buprenorphine doses >24mg show similar efficacy and safety profiles."[58] The study cited in the Petition does not support this statement. The narrative review in the study cites two studies when discussing buprenorphine dosing. The first is a meta-analysis of 31 clinical trials that looks at effectiveness.[59] The narrative review states that this meta-analysis groups studies into ≥16 mg and a flexible daily dose category but does not specifically mention >24 mg or the percentage of patients falling into this category.[60] The other study is the secondary analyses by Hser et al. of a clinical trial discussed above, in which the study authors state that "among patients treated with buprenorphine at the high end of the dose range (30–32 mg/day), retention at 6 months was 60 percent although 30 percent of those still had opioid-positive urine tests, suggesting that even higher doses might be explored in future studies." The Hser et al. study is the only reference specifically mentioning doses >24 mg.

The Petition also cites to a Wong et al. study.[61] The Petition does not rely upon this study in support of the requested labeling change but rather references this study for the position that

[56] Petition at 4 citing to Ahmadi, J, MS Jahromi, D Ghahremani, and ED London, 2018, Single high-dose buprenorphine for opioid craving during withdrawal, Trials, 19(1): 675, doi: 10.1186/s13063-018-3055-z.
[57] Ahmadi et al.
[58] Petition at 4 citing to Shulman, M, JM Wai and EV Nunes, 2019, Buprenorphine Treatment for Opioid Use Disorder: An Overview, CNS Drugs, 33(6):567-580.
[59] Shulman et al. at 7.
[60] Id.
[61] Petition at 4 citing to Wong, J, B Saver, JM Scanlan, LP Gianutsos, Y Bhakta, J Walsh, A Plawman, D Sapienza, and V Rudolf, 2018, Does Maternal Buprenorphine Dose Affect Severity or Incidence of Neonatal Abstinence Syndrome?, J Addict Med, 12(6):435-441, doi: 10.1097/ADM. 0000000000000427. PMID: 29905586.

there is "no relationship between dose and risk of neonatal abstinence syndrome."[62] The results of this study have limited generalizability because the data are only from one medical center and the study has a small sample size of 89 patients.[63] The percentages of pregnancies that resulted in neonatal abstinence syndrome (NAS) were similar and not statistically different between pregnant women taking ≤ 8 mg/day and > 8 mg/day. Further, although the Petition claims that "pregnant women may need higher doses of medications for OUD due to increased volume of distribution and increase hepatic clearance, leading to subtherapeutic plasma concentration,"[64] the Petition's cited study regards NAS and does not provide any adequate clinical or pharmacologic data to support the Petition's statement.[65] Nonetheless, FDA believes that BTOD labeling could be more clear regarding pregnant females needing higher doses of buprenorphine for OUD treatment where the labeling refers to "dosage adjustments." The current BTOD labeling already recognizes that pregnant females may need dosage adjustments, which would include higher doses of buprenorphine (see, e.g., section 8.1 of labeling for Suboxone). However, as explained further in section II.B of this letter, FDA recommends updates to BTOD labeling to clarify that "dosage adjustments" include higher doses based on individual response.

In sum, although these studies provide some evidence suggesting that, generally, higher doses of buprenorphine may be associated with patient outcomes such as longer retention in OUD treatment or less opioid use, the Petition's cited studies are insufficient to support the Petition's requested changes to BTOD labeling.

2. Additional Studies

In addition to reviewing the studies cited in the Petition, the Agency conducted our own extensive review to determine whether there was other evidentiary support for the labeling change requested in the Petition. The Petition makes claims of improved patient outcomes associated with doses greater than 24 mg/day and omits from the requested labeling language the statement currently in BTOD labeling that reads, "dosages higher than 24 mg/6 mg daily have not been demonstrated to provide a clinical advantage."[66] The Petition's requested labeling change also includes the statement, "Evidence suggests that 16mg per day or more may reduce the risk of overdose death more effectively than lower doses."[67] For the sake of completeness, we conducted a literature review for clinical trials and observational studies regarding the effect of doses greater than 24 mg/day and of doses 16 mg/day or greater relative to lower daily dosages. In our review of the literature, we could find no adequate and well-controlled investigations, including clinical trials, to support the Petition's recommended labeling statements.

[62] Petition at 4.
[63] Wong et al.
[64] Petition at 4.
[65] Jones, HE, RE Johnson, DR Jasinski, KE O'Grady, CA Chisholm, RE Choo, M Crocetti, R Dudas, C Harrow, MA Huestis, LM Jansson, M Lantz, BM Lester, and L Milio, 2005, Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome, Drug Alcohol Depend, 79(1):1-10, doi: 10.1016/j.drugalcdep.2004.11.013. PMID: 15943939.
[66] See Petition at 2.
[67] Petition at 1.

Of note, the body of published literature on the relationship between buprenorphine dose and treatment outcomes is rapidly growing. Our literature review included studies published through July 2024;[68] therefore, it does not include studies published more recently, including at least one observational study published in late September 2024.[69] We continuously reevaluate the available evidence and the accuracy of information in BTOD labeling as we become aware of new data.

i. Clinical Trials

We could find no adequate and well-controlled trials evaluating the efficacy of buprenorphine dosages above 24 mg/day from the peer-reviewed literature. Additionally, NDA 020733 for Suboxone (buprenorphine HCl and naloxone HCl) sublingual tablets did not evaluate the efficacy of doses > 24 mg/day.[70]

Further, we did not find any adequate, well-controlled investigations evaluating whether doses "16mg per day or more may reduce risk of overdose death more effectively than lower doses."[71] However, several clinical trials evaluated other outcomes with dosages 16 mg/day or greater.

Three randomized controlled trials evaluated the effect of buprenorphine dosages of 16 mg or greater. Ling et al. conducted a randomized, double blind trial examining the efficacy of various dosages of buprenorphine sublingual solution: 16 mg (approximately 24 mg tablet dose) versus 8 mg (approximately12 mg tablet dose), 4 mg (approximately 6 mg tablet dose) and 1 mg (approximately <2 mg tablet dose) among 736 adult participants meeting Diagnostic and Statistical Manual of Mental Disorders (DSM)-III criteria for opioid dependence.[72] Endpoints included retention in treatment at 16 weeks, urine tests of illicit opioid use, craving scales and global ratings of severity by patients and research staff.[73] Although the results of the trial suggest improved retention in treatment and patterns of urine screens negative for opioids for the 16 mg versus 8 mg groups, these results were not statistically significant.

In the second randomized, double blind trial, the efficacy of 2 mg/day buprenorphine sublingual solution (approximately <6 mg tablet dose) was compared against 8 mg/day buprenorphine sublingual solution (approximately 12 mg tablet dose), 16 mg/day buprenorphine sublingual solution (approximately 24 mg tablet dose), and 16 mg/every other day in 179 adults meeting

[68] In our search for relevant observational studies, we identified additional studies addressed in this letter through PubMed published from January 2013 to July 2024 or cited by articles found in the search.
[69] See, e.g., Axeen S, RL Pacula, JS Merlin, AJ Gordon, and Stein BD, 2024, Association of Daily Doses of Buprenorphine With Urgent Health Care Utilization, JAMA Netw Open, ;7(9):e2435478. doi:10.1001/jamanetworkopen.2024.35478.
[70] We further note that there is no adequate safety data to support chronic administration of an 8 mg daily naloxone dose for a 32 mg/8 mg daily dose of a buprenorphine/naloxone product.
[71] Petition at 1.
[72] Ling, W, C Charuvastra, JF Collins, S Batki, LS Brown Jr, P Kintaudi, DR Wesson, L McNicholas, DJ Tusel, U Malkerneker, JA Renner Jr, E Santos, P Casadonte, C Fye, S Stine, RI Wang, and D Segal, 1998, Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial, Addiction, 93(4):475-86, doi: 10.1046/j.1360-0443.1998.9344753.x. PMID: 9684386.
[73] Id.

criteria for both DSM-III opioid and cocaine dependence over ten weeks.[74] Comparison of the buprenorphine dose groups was not statistically significant for any endpoints, which included non-study drug metabolite concentrations, qualitative urine drug screens, and retention in treatment. We note that the endpoint for retention in treatment was similar for the 16 mg sublingual solution (approximately 24 mg tablet dose) group and the 8 mg sublingual solution (approximately 12 mg tablet dose) group.

The third randomized controlled trial compared the efficacy of buprenorphine sublingual solution 12 mg (approximately 16 mg tablet dose) with 4 mg sublingual solution (approximately 6 mg tablet dose) and various doses of methadone among 116 adults meeting DSM-III criteria for both opioid and cocaine dependence.[75] Of the three randomized clinical trials, this study was the least relevant to the Petition's requested actions because it compared relatively lower dosages and thus, would be the least informative regarding whether dosage above 24 mg/day would result in improved outcomes for patients or whether there is a clinical benefit associated with dosages ≥16 mg/day. Differences in treatment retention favored the 12 mg sublingual solution (approximately 16 mg tablet dose) group compared with the 4 mg sublingual solution (approximately 6 mg tablet dose) group, but these results were not statistically significant. While the 12 mg sublingual solution (approximately 16 mg tablet dose) group showed improvement in some measures of patterns of opioid use compared with the 4 mg sublingual solution (approximately 6 mg tablet dose) group, these endpoints do not conform to those typically used in more recent trials of investigational drug products seeking an indication for opioid use disorder.

ii. Observational Epidemiologic Studies

The observational epidemiologic studies captured in our own literature review focused on patient outcomes (e.g., increased treatment retention or adherence, reduced opioid use, or reduction in overdoses) associated with variably defined higher dosage ranges versus lower ranges of buprenorphine for treatment of OUD. We reviewed 19 published studies, excluding studies cited in the Petition and discussed previously.

[74] Montoya, ID, DA Gorelick, KL Preston, JR Schroeder, A Umbricht, LJ Cheskin, WR Lange, C Contoreggi, RE Johnson and PJ Fudala, 2004, Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence, Clin Pharmacol Ther, 75(1): 34-48.

[75] Schottenfeld, RS, JR Pakes, A Oliveto, D Ziedonis, TR Kosten, 1997, Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse, Arch Gen Psychiatry, 54(8):713-20.

Only three[76] of the 19 studies examined outcomes associated with doses greater than 24 mg/day, and findings were mixed. Two[77] additional studies evaluated doses ≥24 mg/day; however, the most common dose in this category was exactly 24 mg/day, which is already included in the dosage range for maintenance described in current FDA-approved labeling for BTODs.

Many of the remaining studies had findings consistent with statements in the Petition suggesting that "higher" buprenorphine doses, especially doses ≥16 mg/day, may be associated with some patient outcomes related to effectiveness. These studies[78] evaluated outcomes associated with

[76] Clark, RE, JD Baxter, BA Barton, G Aweh, E O'Connell, and WH Fisher, 2014, The impact of prior authorization on buprenorphine dose, relapse rates, and cost for Massachusetts Medicaid beneficiaries with opioid dependence. Health Serv Res, 49(6):1964-79, doi:10.1111/1475-6773.12201; Zhang, K, CM Jones, WM Compton, GP Guy, ME Evans, and ND Volkow, 2023, Association Between Receipt of Antidepressants and Retention in Buprenorphine Treatment for Opioid Use Disorder: A Population-Based Retrospective Cohort Study, J Clin Psychiatry, 83(3), doi:10.4088/JCP.21m14001; Mount, JD, J Sun, A Davis, A Cover, L Sun, C Gannon, M Derenoncourt, G Garrett, R Eyasu, E Ebah, P Bijole, A Greenblatt, K Kattakuzhy, and E Rosenthal, 2024, Dose-specific clinical outcomes in patients with opioid use disorder treated with 24-32 mg/day of buprenorphine, Addiction, doi:10.1111/add.16600.

[77] Chambers, LC, BD Hallowell, AR Zullo, TJ Palva, J Berk, R Gaither, AJ Hampson, FL Beaudoin, and RS Wightman, 2023, Buprenorphine Dose and Time to Discontinuation Among Patients With Opioid Use Disorder in the Era of Fentanyl, JAMA Netw Open, 6(9):e2334540, doi:10.1001/jamanetworkopen.2023.34540; Ferri, M, AJ Finlayson, L Wang, and PR Martin, 2014, Predictive factors for relapse in patients on buprenorphine maintenance, Am J Addict, 23(1):62-7, doi:10.1111/j.1521-0391.2013.12074.x.

[78] Accurso, AJ and DA Rastegar, 2016, The Effect of a Payer-Mandated Decrease in Buprenorphine Dose on Aberrant Drug Tests and Treatment Retention Among Patients with Opioid Dependence, J Subst Abuse Treat, 61:74-9, doi:10.1016/j.jsat.2015.09.004; Binger, KJ, ED Ansara, TM Miles, and SL Schulte, 2020, Relapse rates among veterans on maintenance doses of combination buprenorphine and naloxone for opioid use disorder, Ment Health Clin, 10(3):80-84, doi:10.9740/mhc.2020.05.080; Chambers et al., 2023; Clark et al., 2014; Coker, JL, D Catlin, S Ray-Griffith, B Knight, and ZN Stowe, 2018, Buprenorphine medication-assisted treatment during pregnancy: An exploratory factor analysis associated with adherence, Drug Alcohol Depend, 192:146-149, doi:10.1016/j.drugalcdep.2018.07.042; Mount et al., 2024; Eren, K, J Schuster, A Herschell, D Loveland, G Neimark, M Mihalyo, M Hurford, P Houck, and N Ryan, 2022, Association of Counseling and Psychotherapy on Retention in Medication for Addiction Treatment Within a Large Medicaid Population, J Addict Med, 16(3):346-353, doi:10.1097/adm.0000000000000914; Fareed, A, S Vayalapalli, J Casarella, and K Drexler, 2012, Treatment outcome for flexible dosing buprenorphine maintenance treatment, Am J Drug Alcohol Abuse, 38(2):155-60, doi:10.3109/00952990.2011.643988; Ferri et al., 2014; Jacobs, P, A Ang, MP Hillhouse, AJ Saxon, S Nielson, PG Wakim, BE Mai, LJ Mooney, JS Potter, and JD Blaine, 2015, Treatment outcomes in opioid dependent patients with different buprenorphine/naloxone induction dosing patterns and trajectories, Am J Addict, 24(7):667-75, doi:10.1111/ajad.12288; Kavanagh, K, K Tallian, JA Sepulveda, S Rojas, S Martin, and H Sikand, 2022, Do buprenorphine doses and ratios matter in medication assisted treatment adherence, Ment Health Clin, 12(4):241-246, doi:10.9740/mhc.2022.08.241; Khemiri, A, E Kharitonova, V Zah, J Ruby, and M Toumi, 2014, Analysis of buprenorphine/naloxone dosing impact on treatment duration, resource use and costs in the treatment of opioid-dependent adults: a retrospective study of US public and private health care claims, Postgrad Med, 126(5):113-20, doi:10.3810/pgm.2014.09.2805; Lei, F, MR Lofwall, J McAninch, R Adatorwovor, E Slade, PR Freeman, DC Moga, N Dasgupta, SL Walsh, R Vickers-Smith, and S Slavova, 2024, Higher First 30-Day Dose of Buprenorphine for Opioid Use Disorder Treatment Is Associated With Decreased Mortality, J Addict Med, 18(3):319-326, doi:10.1097/adm.0000000000001300; Lo-Ciganic, WH, JM Donohue, JY Kim, EE Krans, BL Jones, D Kelley, AE James, and MP Jarlenski, 2019, Adherence trajectories of buprenorphine therapy among pregnant women in a large state Medicaid program in the United States, Pharmacoepidemiol Drug Saf, 28(1):80-89, doi:10.1002/pds.4647; Manhapra, A, E Agbese, DL Leslie, and RA Rosenheck, 2018, Three-Year Retention in Buprenorphine Treatment for Opioid Use Disorder Among Privately Insured Adults, Psychiatr Serv, 69(7):768-776, doi:10.1176/appi.ps.201700363; Parran, TV, AG Mace, YJ Dahan, CA Adelman, and M Kolganov, 2017, Buprenorphine/Naloxone Maintenance Therapy: an Observational Retrospective Report on the Effect of Dose on 18 months Retention in an Office-Based Treatment Program, Subst Abuse, 11:1178221817731320,

various measures of higher buprenorphine dosage (≥16 mg/day) relative to lower dosages. These included multiple reasonably controlled observational studies using a variety of data sources and analytic approaches suggesting that doses ≥16 mg/day may contribute to longer retention in treatment compared to doses of <16 mg/day. We note that this comparison group included doses lower than or at the lower end of the recommended dosing range for maintenance (e.g., buprenorphine doses of 2-8 mg/day). There were mixed results across studies that assessed whether doses ≥16 mg/day were associated with reduced (non-buprenorphine) opioid use compared to <16 mg/day.

Our review identified one recently published study that found that first 30-day buprenorphine dose >16 mg/day was associated with a significantly lower risk of fatal overdose and all-cause mortality in the subsequent year, compared to patients receiving ≤8 mg/day.[79] Although these findings are generally consistent with higher buprenorphine dose being associated with a reduced risk of overdose death, the study does not directly evaluate the accuracy of the Petition's proposed language that doses ≥16mg/day may reduce risk of overdose death more effectively than lower doses (which we interpret as <16mg/day). The study was also subject to a number of limitations, and results from this single, observational study are insufficient to support the labeling language requested by the Petition.

Generally, these studies had substantial methodologic limitations. Described below are some key limitations we identified.

- Most of the studies had the potential for reverse causation, whereby exposure (e.g., maximum buprenorphine dose) and outcome (e.g., retention) are inherently related such that patients who have been in treatment longer have more opportunity to be exposed to higher doses. The dose trajectories of patients were generally not described, making it difficult to assess the severity and direction of this potential bias.
- Many of these studies did not account for fundamental confounders such as age and gender, and most were unable to account for important but more challenging factors to measure, such as socioeconomic status or OUD severity. These factors may influence both the dose received and treatment outcomes, and if not sufficiently measured and adjusted for, may confound the findings in unpredictable directions.
- Studies using administrative claims databases were vulnerable to bias of unpredictable direction due to misclassification of both the drug exposure (i.e., dispensed prescriptions not captured, or inaccurate dose or days' supply) and retention or adherence outcomes, when based on prescription fill data alone. Depending on insurance coverage restrictions, patients may need to pay for part or all their buprenorphine prescription, particularly for higher doses, using cash or coupon payments which would not be captured in insurance claims data.

doi:10.1177/1178221817731320; Selitsky, L, C Nordeck, A Truong, D Agus, and ME Buresh, 2023, Higher buprenorphine dose associated with increased treatment retention at low threshold buprenorphine clinic: A retrospective cohort study, J Subst Use Addict Treat, 147:208981, doi:10.1016/j.josat.2023.208981; Stein, MD, P Cioe, and PD Friedmann, 2005, Buprenorphine retention in primary care, J Gen Intern Med, 20(11):1038-41. doi:10.1111/j.1525-1497.2005.0228.x; Zhang et al, 2023.

[79] Lei et al., 2024.

- None of the studies accounted for changes in buprenorphine dosing during treatment, such as when a provider increases the dose for a limited time to manage withdrawal, cravings, or ongoing illicit opioid use. Marginal structural models are one analytic method that can be used for situations where exposure changes over time in response to time-dependent covariates,[80] but none of the studies employed this or similar advanced techniques to account for time-dependent covariates.
- Data sources do not capture information on prior treatment provided by opioid treatment programs, including when transferring from methadone to buprenorphine or from inpatient/residential treatment to outpatient treatment.
- Small sample sizes were a limitation in multiple studies, and pre-specified power calculations were rarely reported. Studies with findings that were not statistically significant may have been insufficiently powered to detect a clinically meaningful difference or association. The issue of small sample sizes is especially problematic when assessing outcomes in patients on buprenorphine doses >24 mg/day because only a small percentage of patients received doses >24 mg/day.
- Most of these studies used older data, with less than half of studies including any data after 2016 and a minority with a study period that included only 2016 or later, which is an important consideration given changes in the illicit drug supply after 2016.
- Dosage comparisons were often not those that would be needed to inform labeling changes indicating a clinical advantage of doses ≥16 mg/day compared to <16 mg/day or doses ≥24 mg/day compared to <24 mg/day. For example, higher dosages (e.g., greater than 24 mg/day) were often compared with much lower dosage groups (e.g., 8-16 mg/day), rather than to the next highest dosage or dosage category (e.g., 24 mg/day, or >16-24 mg/day).

Additionally, in our analysis of the existing literature, we encountered challenges with synthesizing results across studies due to heterogeneity of outcome and dosage category definitions. For example, measures of opioid use (i.e., use of opioids other than for OUD treatment) and adherence were usually defined as a self-report of opioid use and/or positive urine drug screening test, although some studies also included prescription claims for opioids other than buprenorphine as measures of return to opioid use. Measures of retention or the end of treatment was sometimes variably defined as 30 or 60 days without a prescription claim or failing to show up for treatment for a set number of days. Additionally, studies had widely varying lengths of follow-up time and buprenorphine dosage category definitions (e.g., initial dose, mean or median dose dispensed, highest dose dispensed).

iii. Summary

In summary, we found no adequate and well-controlled investigations evaluating the efficacy of doses >24 mg/day or establishing that "16mg per day or more may reduce risk of overdose death more effectively than lower doses." We found multiple observational studies evaluating doses 16 mg/day or greater and some evaluating doses >24 mg/day. The available observational evidence is insufficient to determine whether, overall, doses >24 mg/day improve patient outcomes (e.g., longer retention in treatment, measures of opioid use) compared to doses 24

[80] Robins, JM, MA Hernan, and B Brumback B, 2000, Marginal Structural Models and Causal Inference in Epidemiology, Epidemiology, 11 (5): 550-556.

mg/day or lower. While studies evaluating buprenorphine doses ≥16 mg/day may provide helpful insights into potential improvements in patient outcomes, such as retention in OUD treatment, opioid use, and overdose, these studies do not support the Petition's requested change to BTOD labeling regarding reduced risk of overdose.

We note that the findings are generally consistent with current BTOD labeling recommending a target dose of 16 mg/day, language which was intended to encourage prescribers to move quickly from low starting doses used for induction to higher doses, titrated to clinical effectiveness. We also emphasize that the current BTOD labeling already describes the need for individualized dosing based on clinical response, suggesting that higher doses may be necessary for some patients to have outcomes comparable to those experienced by other patients on lower doses. Therefore, the lack of evidence that study populations have better outcomes on doses ≥16 mg/day compared to <16 mg/day or doses >24 mg/day compared to ≤24 mg/day to support the Petition's proposed labeling changes does not preclude the possibility that individual patients may experience improved outcomes on higher doses of this medication.[81]

B. Recommendations To Update BTOD Labeling

Based on all the information we have reviewed, including studies cited in the Petition and studies we searched and analyzed, we have determined that the Petition's suggested labeling revisions are not supported by existing scientific literature. Accordingly, the Petition's suggested labeling revisions are not appropriate, and FDA cannot unilaterally update approved drug labelingin any case. However, the Petition has helped illustrate that the current labeling for BTODs may be

[81] The Petition also raised concerns about the potential diversion of buprenorphine (Petition at 5). BTODs are schedule III controlled substances under the CSA, and, as drugs with abuse potential, are subject to misuse, abuse, and diversion. Because the Petition raised the issue of diversion, we reviewed the articles cited in the Petition and conducted our own literature review of studies on this issue, although we recognize that diversion considerations implicate the jurisdiction of other federal agencies. See, e.g., Zosel, A, BB Bartelson, E Bailey, S Lowenstein, and R Dart, 2013, Characterization of adolescent prescription drug abuse and misuse using the Researched Abuse Diversion and Addiction-related Surveillance (RADARS(®)) System, J Am Acad Child Adolesc Psychiatry, 52(2):196-204.e2, doi:10.1016/j.jaac.2012.11.014; Soyka, M, 2013, Buprenorphine and buprenorphine/naloxone intoxication in children - how strong is the risk?, Curr Drug Abuse Rev, 6(1):63-70, doi:10.2174/18744737112059990010; Post, S, HA Spiller, MJ Casavant, T Chounthirath, GA Smith, 2018, Buprenorphine Exposures Among Children and Adolescents Reported to US Poison Control Centers, Pediatrics, 142(1), doi:10.1542/peds.2017-3652; Tanz, LJ, CM Jones, NL Davis, WM Compton, GT Baldwin, B Han, and ND Volkow, 2023, Trends and Characteristics of Buprenorphine-Involved Overdose Deaths Prior to and During the COVID-19 Pandemic, JAMA Netw Open, 6(1):e2251856, doi:10.1001/jamanetworkopen.2022.51856; Walley, AY, D Bernson, MR Larochelle, TC Green, L Young, and T Land, 2019, The Contribution of Prescribed and Illicit Opioids to Fatal Overdoses in Massachusetts, 2013-2015, Public Health Rep, 134(6):667-674, doi:10.1177/0033354919878429; Simpson, KJ, MT Moran, ML Foster, DT Shah, DY Chung, SD Nichols, KL McCall, and BJ Piper, 2019, Descriptive, observational study of pharmaceutical and non-pharmaceutical arrests, use, and overdoses in Maine, BMJ Open, 9(4):e027117, doi:10.1136/bmjopen-2018-027117; Wightman, RS, J Perrone, R Scagos, M Krieger, LS Nelson, and BDL Marshall, 2021, Opioid Overdose Deaths with Buprenorphine Detected in Postmortem Toxicology: a Retrospective Analysis, J Med Toxicol, 17(1):10-15, doi:10.1007/s13181-020-00795-3; Bishop-Freeman, SC, LW Friederich, MS Feaster, JS Hudson, 2021, Buprenorphine-Related Deaths in North Carolina from 2010 to 2018, J Anal Toxicol, 45(8):780-791, doi:10.1093/jat/bkab073. Although we acknowledge that increasing medication supplies for drugs with abuse potential are often correlated with increased risks of misuse, abuse, diversion, and associated adverse outcomes, including overdose and death, based on our review, there is insufficient evidence to conclude that daily dose of buprenorphine is associated with an increased risk of diversion.

perceived as a barrier to prescribing or dispensing buprenorphine dosages higher than 24 mg/day for certain patients, and even dosages higher than 16 mg once daily, and that the language in the labeling may have other implications, such as being used to limit insurance coverage for higher dosages. The Petition specifically refers to a statement in BTOD labeling that reads, "dosages higher than 24 mg/6 mg daily have not been demonstrated to provide a clinical advantage," to suggest that healthcare providers may not be prescribing dosages above 24 mg daily.[82] The reluctance of some healthcare practitioners to prescribe buprenorphine daily dosages of 24 mg or higher, and even 16 mg in some instances, may be based on a misinterpretation of the labeling that 16 mg or 24 mg once daily dosages are maximum dosages. The Petition also claims that state Medicaid programs, state medical boards, and insurance carriers are setting "arbitrary buprenorphine dose limits" and cites to the Tennessee Department of Health guidelines that set documentation and other requirements for buprenorphine prescriptions greater than 16 mg/daily for greater than a month.[83] We have heard similar concerns raised by other interested parties.[84]

In light of what we have learned from the Petition and other interested parties, we believe that certain statements in BTOD labeling can be modified because the labeling for these products may be misinterpreted by some as establishing a maximum dosage when none exists. These recommended changes to the labeling would provide further clarity to BTOD labeling. FDA is concerned that misinterpretation of these labeling statements may be adversely impacting patients' access to BTODs. Therefore, we are today issuing a *Federal Register* notice titled, Modifications to Labeling Buprenorphine-Containing Transmucosal Products for the Treatment of Opioid Dependence to encourage the submission of supplemental NDAs (labeling supplements) to modify the labeling statements for BTODs as described in the notice.[85]

In the notice, FDA recommends the following specific changes to the maintenance dosage recommendations in the "Dosage and Administration" section of the most recent approved BTOD labeling:[86]

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[82] Petition at 3.
[83] Petition at 5.
[84] In May 2023, the Reagan-Udall Foundation hosted a 2-day public meeting with FDA and SAMHSA, entitled "Considerations for Buprenorphine Initiation and Maintenance Care," in which interested parties attending the public meeting expressed concerns similar to those raised in the Petition about perceived buprenorphine maximum doses. Meeting materials and transcripts available at https://reaganudall.org/news-and-events/events/considerations-buprenorphine-initiation-and-maintenance-care. On December 11, 2023, SAMHSA, FDA, and the National Institute on Drug Abuse (NIDA) hosted a listening session to discussion the medical need, emerging data, and barriers to accessing higher doses of buprenorphine in the context of high potency synthetic opioid exposure, and concerns were raised about a perceived dosage "cap at 24 mg/day" that is "set to the FDA label" for BTODs. Meeting summary can be accessed at https://store.samhsa.gov/sites/default/files/high-dose-buprenorphine-report-pep24-02-013.pdf.
[85] Although not directly requested in the citizen petition, the notice also makes recommendations to update the "Pregnancy" subsection of the "Use in Specific Populations" section of the labeling, in part, to be consistent with the changes recommended for the "Dosage and Administration" section of the labeling.
[86] Some BTOD products contain buprenorphine only and others are fixed combinations containing buprenorphine and naloxone. Further, some products containing buprenorphine may provide equivalent buprenorphine exposure at alternate doses (e.g., equivalent to 16 mg or equivalent to 24 mg buprenorphine in SUBUTEX and SUBOXONE) due to differences in formulation. Accordingly, where the notice recommends changes to the labeling, application holders of these BTOD products should update the labeling with appropriate product-specific information, including the appropriate dose(s) specific to their products.

> After treatment induction to the recommended dose of [equivalent 16 mg buprenorphine **OR** equivalent 16 mg/4 mg buprenorphine/naloxone] per day, dosing should be further adjusted based on the individual patient and clinical response. The maintenance dose of [DRUG NAME] is generally in the range of [equivalent 4 mg buprenorphine **OR** equivalent 4 mg/1 mg buprenorphine/naloxone] to [equivalent 24 mg buprenorphine **OR** equivalent 24 mg/6 mg buprenorphine/naloxone] per day. Dosages higher than [equivalent 24 mg buprenorphine **OR** equivalent 24 mg/6 mg buprenorphine/naloxone] daily have not been investigated in randomized clinical trials but may be appropriate for some patients.

FDA further recommends the following specific change under the "Dose Adjustment during Pregnancy and the Postpartum Period" subheading under the "Clinical Considerations" heading in the "Pregnancy" subsection of the "Use in Specific Populations" section in BTOD labeling:

> Dosage adjustments of buprenorphine, such as using higher doses, may be required during pregnancy, even if the patient was maintained on a stable dose prior to pregnancy. Dosing should be based on individual response, and withdrawal signs and symptoms should be monitored closely and the dose adjusted as necessary.

FDA recommends these changes given the concerns raised regarding the maintenance dosage recommendations in the "Dosage and Administration" section of BTOD labeling in that it may not be clear from the most recent approved labeling that certain populations, including pregnant females, may need a higher dosage of buprenorphine.

C. Dear Stakeholder Letter

In addition to the Petition's proposed labeling update, the Petition requests that FDA "[i]ssue a drug safety communication (DSC) to providers highlighting the potential clinical benefit of sublingual buprenorphine doses ≥16mg/day in patients with OUD."[87] As mentioned in section I.C of this letter, a DSC is one tool used by the Agency to communicate important new and emerging safety information to the public. The "potential clinical benefit" of buprenorphine doses ≥16 mg/day is not a safety issue. Further, communicating a message to the public of the "potential clinical benefit" of buprenorphine doses ≥16 mg/day is not appropriate in any case because, as we explain above, existing evidence in the scientific literature does not support a conclusion that buprenorphine dosages ≥16 mg/day provide a clinical benefit over buprenorphine doses below 16 mg daily. Accordingly, the Petition's request that FDA issue a DSC is denied.

However, the Agency finds that a communication to the public may provide clarification on the recommended daily dose for BTODs, because we have heard from the public that there is a perception that the labeling for these products includes a maximum dose for maintenance treatment when none exists. Accordingly, today, we issued a "Dear Stakeholder Letter" informing the public that the labeling does not include any maximum dose and that prescribers should make dosing decisions based on the individual patient and clinical response. This letter also informs interested parties that FDA has issued a *Federal Register* notice to encourage the submission of labeling supplements to modify the labeling statements for BTODs as described in the notice. To the extent that the Petition asks FDA to issue a communication to stakeholders,

[87] Petition at 1.

including, healthcare practitioners, to emphasize that the BTOD labeling does not include a maximum dosage, the request is granted.

III. CONCLUSION

In summary, the Petition is granted to the extent that the Agency has taken affirmative steps to facilitate changes to BTOD labeling through today's issuance of a *Federal Register* notice encouraging the sponsors of BTOD products to submit supplements for the labeling clarifications described in the notice. The Petition is denied with respect to the specific labeling language requested. The Petition is further granted to the extent that the Petition seeks FDA to issue a communication to stakeholders, including healthcare practitioners, to emphasize that BTOD labeling does not include a maximum dosage, which may result in increased access to higher dosages if deemed necessary based on the individual patient and clinical response. The Petition is denied to the extent that it requests FDA to use a DSC as the vehicle for that communication.

Sincerely,

Douglas C. Throckmorton -S

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