NDA 020732/S-023
NDA 020733/S-027
NDA 022410/S-039

**SUPPLEMENT APPROVAL**

Indivior Inc.
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Attention Rachel Capone
Manager, Regulatory Affairs

Dear Ms. Capone:

Please refer to your supplemental new drug applications (sNDAs) dated and received June 18, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SUBUTEX (buprenorphine) sublingual tablets (NDA 020732/S-023), SUBOXONE (buprenorphine and naloxone) sublingual tablets (NDA 020733/S-027), and SUBOXONE (buprenorphine and naloxone) sublingual film (NDA 022410/S-039).

These Prior Approval sNDAs proposed modifications to the approved risk evaluation and mitigation strategy (REMS) for SUBUTEX sublingual tablets, SUBOXONE sublingual tablets, and SUBOXONE sublingual film.

We have completed our review of these supplemental applications, as amended and they are approved effective on the date of this letter.

## RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for SUBOXONE (buprenorphine and naloxone) sublingual film was originally approved on August 30, 2010. The REMS for SUBUTEX (buprenorphine) sublingual tablets and the REMS for SUBOXONE (buprenorphine and naloxone) sublingual tablets were originally approved on December 22, 2011. The most recent modification was approved on October 26, 2018. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS consists of modifying the REMS Document to the new format in accordance with the October 2017 *Draft Guidance: Format and Content of a REMS Document Guidance for Industry*. In addition to the modification described above, changes to the supporting document and assessment plan were also included in the submission.

Your proposed modified REMS, submitted on June 18, 2019, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on August 31, 2012.

The revised REMS assessment plan must include, but is not limited to, the following:

1. An evaluation of patients' understanding of the serious risks of SUBOXONE sublingual film.
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
3. A report on failures to adhere to distribution and dispensing requirements for the Medication Guide, and corrective actions taken to address noncompliance.
4. A survey of prescribers' understanding of the serious risks of SUBOXONE sublingual film and the:

    a) need for appropriate patient monitoring
    b) need for patient adherence to conditions of safe use
    c) need to check that patients are using the drug appropriately and making adequate progress towards treatment goals
    d) need to make sure prescriptions are provided in amounts commensurate with patient stability
    e) importance of psychosocial support services
    f) The results of the prescriber survey will be stratified by stage of treatment (i.e., those initiating treatment [month 1] vs. established patients [month 2+]). The stratification will be applied to the analysis of the 12 possible steps prescribers use to reduce inappropriate use or diversion in their practices.
    g) Specific measures that will be taken to increase awareness if surveys of prescribers indicate that prescriber awareness is not adequate

5. A survey of pharmacists' understanding of the serious risks of SUBOXONE sublingual film and the need for patient adherence to conditions of safe use.
6. An analysis to evaluate SUBOXONE sublingual film utilization patterns including frequency of office visits, amount dispensed in prescriptions to new patients and other indicators of adherence to practices important to safe use. The analysis of utilization patterns (frequency of office visits per patient, amount of medication dispensed in prescriptions, etc.) will be stratified by stage of treatment (i.e., new [month 1] vs. established patients [month 2+]).
7. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose and addiction and any intervention taken resulting from signals of abuse, misuse, overdose and addiction. Surveillance data are to be drawn from multiple sources and are to place a special focus on pediatric exposures.

The SUBOXONE/SUBUTEX REMS will undergo periodic review to evaluate the effectiveness of the strategies and tools in accomplishing the goals and objectives of the REMS. Appropriate revisions to the REMS will be proposed based on the evaluations. Based on the monitoring and evaluation of these elements to assure safe use, Indivior will take reasonable steps to improve implementation of these elements, such as suggesting changes to the prescriber or pharmacist brochures or mailing an additional letter to healthcare providers (HCPs) based on which specific risks messages seem to have low understanding.

### *Medication Guide Distribution Audits*

Indivior will periodically assess the distribution and dispensing of the SUBOXONE sublingual film, Authorized Generic of SUBOXONE sublingual film, SUBOXONE sublingual tablet, and SUBUTEX sublingual tablet Medication Guide in accordance with 21 CFR 208.24. Periodic audits of the packaging facility will be conducted to monitor compliance with inclusion of the Medication Guide within the product packaging. The Knowledge, Attitudes, and Behavior (KAB) surveys described in Section 4.2.12 below will also assess this by querying patients about whether they received a Medication Guide when their prescription for SUBOXONE Sublingual film and Authorized Generic of SUBOXONE sublingual film was dispensed. Failures to adhere to Medication Guide distribution and dispensing requirements will be identified and appropriate actions will be implemented to address non-compliance. This information will be provided in the regular assessment reports for the REMS.

### *Surveillance and Epidemiology*

Epidemiology and surveillance data reporting reflects emails Indivior received from the FDA on 14 JAN 2019, 19 MAR 2019, 24 SEP 2019, and 22 NOV 2019, and referenced in the REMS Assessment Acknowledgement Letter received on 02 AUG 2019.

## Data Sources

As part of the REMS program, Indivior will conduct analysis and summary of surveillance/epidemiologic data on abuse, misuse, overdose (mortality), and addiction.

These data sources include:

- Researched Abused, Diversion and Addiction-Related Surveillance (RADARS®) System:
  - Poison Control Centers
  - Treatment Centers - Survey of Key Informants' Patients (SKIP)/Opioid Treatment Program (OTP)

  - Drug Diversion

- National Forensic Laboratory Information System (NFLIS)
- National Survey of Drug Use (NSDUH)
- National Survey of Substance Abuse Treatment Services (N-SSATS)
- Treatment Episodes Dataset (TEDS)
- Medical Examiners Data
- Assessment of Adherence in Medical Records/Administrative Claims - Feasibility Assessment
- Literature Review

### Researched Abuse, Diversion and Addiction Related Surveillance (RADARS®) System

The RADARS System provides post-marketing surveillance of prescription medication abuse, misuse, and diversion to pharmaceutical companies, regulatory agencies, and policy making organizations. The RADARS System is comprised of multiple independent surveillance programs which gather data from several unique populations along the spectrum of the drug abuse pathway.[i]

#### *RADARS System Poison Center*

The RADARS System Poison Center Program obtains data from participating poison centers, which manage exposure calls from individuals within the general population and from HCPs who are seeking advice regarding potential toxic exposures, including exposures to prescription opioids.[ii] Poison Center Program data collected through the RADARS System provide an estimate of change in intentional abuse, misuse, and deaths associated with these drugs. The Poison Center Program collects data from 50 of the 55 regional US poison centers in 48 states.

**Objective**

- To examine trends in buprenorphine and other opioid exposures reported to US Poison Centers.

**Outcomes**

- Intentional abuse exposures
- Intentional misuse exposures
- Pediatric (ages 0-5 years) unintentional general exposures
- Major medical outcome, hospitalization, or death

**Measures**

- Rate per population
- Utilization based rate (e.g., dosing unit dispensed)
- Proportion of SUBOXONE intentional cases (i.e., intentional abuse, intentional misuse, suspected suicide, intentional unknown) that also involved benzodiazepines
- Number of unspecified abuse cases for buprenorphine

**Buprenorphine Categorizations**

- Any buprenorphine (Active Pharmaceutical Ingredient [API])
- All single ingredient tablets
- All combination tablets
- All combination film products
- SUBOXONE sublingual film
- Authorized Generic of SUBOXONE sublingual film
- Suboxone sublingual tablets
- Subutex sublingual tablets

*Note: It is not possible to differentiate Authorized Generic of SUBOXONE sublingual film in all RADARS Systems; this category will be included when feasible.*

**Comparators (API)**

- Hydrocodone
- Methadone
- Oxycodone

**Analysis**

- Quarterly and annual population rates and utilization-based rates will be calculated. Results will be presented graphically with modeled trend lines and 95% confidence intervals going back to 2011; tabular data for case counts and rates will also be provided. No formal statistical comparisons will be conducted. For all tables and figures, the total number of individuals for each data point will be included where applicable. Additionally, case narratives will be provided for all fatal exposure cases involving SUBOXONE in the RADARS Poison Center Program. As appropriate, for utilization-based analyses of methadone, provide a sensitivity analysis that accounts for methadone's unique distribution mechanism.

### *RADARS System Treatment Center Programs*

The Treatment Center Programs Combined includes data from two distinct RADARS System programs: The Opioid Treatment Program and the Survey of Key Informants' Patients Program (OTP/SKIP).[iii,iv]

The Opioid Treatment Program gathers data from 71 participating medication-assisted treatment programs (public and private) in 33 states yielding approximately 7,000 survey respondents annually. Patients enrolling at these treatment centers are asked to voluntarily complete an anonymous questionnaire with items about primary drug of abuse, sources of drug acquisition, use in the month prior to treatment, and routes of abuse.

The Survey of Key Informants' Patients Program gathers data from a key informant network of 154 treatment programs yielding approximately 3,000 survey respondents annually from 47 states. The patients who seek treatment at primarily private substance abuse treatment programs are recruited by key informants to voluntarily complete an anonymous questionnaire with items about primary drug of abuse, sources of drug acquisition, use in the month prior to treatment, and routes of abuse.

These two programs use the same core data collection form, enabling data to be combined, and complement each other by providing information from patients entering both private and public opioid use disorder treatment programs.

**Objective**

- To examine trends in the abuse of buprenorphine vs. comparators and to characterize the route of abuse profile for SUBOXONE among individuals entering substance abuse treatment centers.

**Outcome**

- Past month abuse

**Measures**

- Rate per population
- Utilization based rate (e.g., dosing unit dispensed)
- Route of abuse profiles for SUBOXONE sublingual film and comparators (proportion of abusers who report abusing it via injection, insufflation, or other routes)
  - The number and percent of respondents who report multiple routes of abuse (i.e., respondents with multiple responses regarding routes of abuse)
- Proportion of SUBOXONE abusers who report that buprenorphine is their primary drug of abuse

**Buprenorphine Categorizations**

- Any buprenorphine (API)
- All single ingredient tablets
- All combination tablets
- All combination film products
- SUBOXONE sublingual film
- Authorized Generic of SUBOXONE sublingual film
- SUBOXONE sublingual tablets
- SUBUTEX sublingual tablets

**Comparators (API)**

- Hydrocodone
- Methadone
- Oxycodone

**Analysis**

- Quarterly and annual population rates and utilization-based rates (i.e., rate per dosing units dispensed) will be calculated for buprenorphine and comparators as well as for buprenorphine product categories. Results will be presented graphically with modeled trend lines and 95% confidence intervals going back to 2011; tabular data for case counts and rates will also be provided. For all tables and figures, the total number of individuals for each data point will be included where applicable. No formal statistical comparisons will be conducted. As appropriate, for utilization-based analyses of methadone, provide a sensitivity analysis that accounts for methadone's unique distribution mechanism.

### *RADARS System Drug Diversion*

The Drug Diversion Program provides surveillance data on the diversion of prescription drugs by conducting a quarterly survey of drug diversion investigators.[v] Drug diversion investigators include municipal police departments, multi-jurisdictional drug task forces, county sheriffs' departments, pharmaceutical boards and departments of health. Drug diversion investigators submit data on the number of documented drug diversion cases within their jurisdiction for specific prescription drugs of interest.

**Objective**

- To examine trends in the diversion of buprenorphine vs. comparators.

**Outcome**

- Diversion cases

**Measures**

- Rate per population
- Utilization based rate (e.g., dosing unit dispensed)

**Buprenorphine Categorizations**

- Any buprenorphine (API)
- All single ingredient tablets
- All combination tablets
- All combination film products
- Suboxone sublingual film
- Authorized Generic of SUBOXONE sublingual film
- SUBOXONE sublingual tablets
- SUBUTEX sublingual tablets

**Comparators (API)**

- Hydrocodone
- Methadone
- Oxycodone

**Analysis**

- Background information, including the agency type, the jurisdiction, the number of quarters providing completed surveys, and the population within the jurisdiction will be provided. Information on the number of investigators working on drug diversion cases and the number of new cases of prescription drug diversion will also be included to provide information on drug activity.
- Quarterly and annual population rates and utilization-based rates will be calculated. Results will be presented graphically with modeled trend lines and 95% confidence intervals going back to 2011; tabular data for case counts and rates will be provided in an appendix. No formal statistical comparisons will be conducted.
- For all tables and figures, the total number for each data point will be included where applicable. As appropriate, for utilization-based analyses of methadone, provide a sensitivity analysis that accounts for methadone's unique distribution mechanism.

## Internet Monitoring of Media Reports

A third party is utilized to monitor any news media reports related to the abuse, misuse and diversion of buprenorphine.

## National Forensic Laboratory Information System (NFLIS)

The National Forensic Laboratory Information System (NFLIS) is a program of the DEA, Diversion Control Division, which systematically collects drug identification results and associated information from drug cases submitted to and analyzed by Federal, State, and local forensic laboratories. These laboratories analyze controlled and noncontrolled substances secured in law enforcement operations across the country. As of 2017, the participation rate (defined as percentage of national drug caseload represented by laboratories who have joined NFLIS) was 98%, with 50 state and 101 local/municipal lab systems, representing 277 individual labs.[vi] Federal data from the DEA and US Customs and Border Protection (CBP) laboratories is also included.

NFLIS results are made available through mid-year and annual reports. These reports provide information on the total number of buprenorphine drug reports and cases analyzed as well as regional results. The NFLIS reports do not include information on specific products but do include information at the API level. The statistical methodology is provided as an Appendix to each report.

**Objective**

- To describe the drug seizure counts and utilization-adjusted rates for buprenorphine and comparators.

**Outcomes**

- Drug reports (drug-level data)
- Drug cases (case-level data, which typically describes all drugs identified within a drug-related incident)

  Note: per NFLIS report, a small proportion of laboratories may assign a single case number to all drug submissions related to an entire investigation.

**Measure**

- Utilization-based rate (e.g., dosing units dispensed)

**Buprenorphine Categorization**

- Buprenorphine (API)

**Comparators (API)**

- Hydrocodone
- Methadone
- Oxycodone

**Analysis**

- All drug reports and drug case data are obtained from published Annual Reports, including the most recent annual report available before the end of the applicable SUBOXONE/SUBUTEX REMS Assessment Report reporting period, and a minimum of 5 years historical data. References to any tables used will be included. Utilization data are obtained from a separate data source that provides estimates of national drug utilization. Utilization based rates are calculated by dividing the number of cases by the total dosing units dispensed in that year. Methodology and definitions of terms will be provided. For all tables and figures, the total number for each data point will be included where applicable. As appropriate, for utilization-based analyses of methadone, provide a sensitivity analysis that accounts for methadone's unique distribution mechanism.

### National Survey on Drug Use and Health (NSDUH)

The NSDUH produces prevalence estimates for indicators of substance use and mental health among people aged 12 years old or older in the civilian, noninstitutionalized population of the US (https://www.datafiles.samhsa.gov/study-series/national-survey-drug-use-and-health-nsduh-nid13517). Results can be weighted to provide a nationally representative estimate.

Assessment of the use and misuse of buprenorphine was added to the 2015 NSDUH. Use of prescription drugs is defined as (a) the use of one's own prescription medication as directed by a doctor. Misuse of prescription drugs is defined as use in any way not directed by a doctor, including use without a prescription of one's own medication; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.

Consistent with NSDUH methodology, respondents will be classified as having a past-year Opioid Use Disorder if they had either a heroin use disorder (i.e., dependence or abuse) or pain reliever use disorder related to their misuse of prescription pain relievers in the past year, or if they had both disorders.

The reason for misuse is based on answers to questions about respondents' reasons for misusing pain relievers for their last misuse. Respondents can report more than one reason, and if they report more than one reason, they are also asked to report the main reasons. The reasons for misuse include to relieve pain, to relax, to experiment, to get high, for sleep, for emotions, for other drug effect, because hooked, or for some other reason. Reasons for misuse for a specific product are only asked if that product was the last prescription pain reliever that was misused. Therefore, only a subset of those who report misuse of a specific product will provide information on reasons for misuse of that product.

**Objective**

- To describe buprenorphine, use and misuse in a nationally representative sample of individuals 12 and older, as well as reason for misuse. Results will be stratified by Opioid Use Disorder.

**Outcomes**

- Use
- Misuse
- Reasons for buprenorphine misuse

**Measures**

- Prevalence of use and misuse

**Buprenorphine Categorization**

- Buprenorphine (API)
- Suboxone
- Buprenorphine (generic)
- Buprenorphine plus naloxone (generic) (select years only)

**Comparators (API)**

- Hydrocodone
- Methadone
- Oxycodone
- Oxymorphone
- Fentanyl
- Morphine
- Tramadol

**Analysis**

- NSDUH data will be obtained from published annual reports and public use datasets available on or before the end of the applicable SUBOXONE/SUBUTEX REMS Assessment Report reporting period. References to any tables used will be included. The prevalence of use and misuse of buprenorphine (API) and comparators will be obtained from published annual reports and/or public use data files. Prevalence rates for buprenorphine misuse will be stratified by Opioid Use Disorder using public use data files. The reason for misuse of specific buprenorphine products (e.g., SUBOXONE) will be obtained from public use data files and will be presented overall and stratified by presence of Opioid Use Disorder. For all tables and figures, the total number of individuals for each data point will be included where applicable.

### National Survey of Substance Abuse Treatment Services (N-SSATS)

The N-SSATS is an annual census of facilities providing substance abuse treatment.[vii] Conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA), the N-SSATS is designed to collect data on the location, characteristics and use of alcohol and drug abuse treatment facilities and services throughout the 50 states, the District of Columbia, and other US jurisdictions. Facilities include both private (for-profit and non-profit) as well as government facilities, and cover inpatient, residential (non-hospital), and outpatient treatment. Data are provided as part of the annual reports.

The N-SSATS does not collect data on misuse of buprenorphine but collects treatment facilities information and the number of clients treated with buprenorphine as medication-assisted therapy.

**Objective**

- To describe medication-assisted therapy with buprenorphine at national treatment facilities.

**Outcomes**

- Facilities providing buprenorphine
- Clients receiving buprenorphine

**Measures**

- Proportion of facilities providing any buprenorphine
- Number of clients receiving buprenorphine
  - Overall
  - By program type
    - Opioid Treatment Program (OTP)
    - Non-OTP facilities

**Buprenorphine Categorization**

- Buprenorphine (API, for Medication Assisted Therapy)

**Analysis**

- All treatment admission data are from published Annual Reports, including the most recent annual report available before the end of the applicable SUBOXONE/SUBUTEX REMS Assessment Report reporting period and a minimum of 5 years historical data. Buprenorphine utilization data, which will be provided as context for any changes to the trends in facilities providing clients receiving buprenorphine treatment over time, are obtained from a separate data source that provides estimates of national drug utilization. References to any

tables used will be included. For all tables and figures, the total number for each data point will be included where applicable.

### Literature Surveillance

A summary and comment/critique of the past 5 years of published observational studies on buprenorphine prescribing practices, misuse, abuse and unintentional overdose will be provided. Investigations of vulnerable populations or those of special interest such as adolescents, pregnancy/fetal exposure, incarcerated or parolee/probationers will be highlighted. Unless accompanied by a review or analysis that can be generalized to a wider audience, editorials, case reports, and case series will not be the focus of this critique.

### Assessment of Adherence in Medical Records/Administrative Claims - Feasibility Assessment

The feasibility of medical records (administrative claims data and electronic medical records) to evaluate adherence to (and best practices for) the Appropriate Use Checklist will be explored and summarized as new information is available.

### Mortality Data

The Centers for Disease Control and Prevention (CDC) Drug-Involved Mortality (DIM) data will be utilized to provide national-level information on buprenorphine involved fatal overdoses. The study period for mortality analyses will be 2010 through the most recent data available. Typically, data are available 7-9 quarters following the end of a calendar year. Drug term assignment is done by manual adjudication of death certificates by experts at the CDC; all mentions are checked against the term list. One consistent definition and set of ICD-10 codes is utilized to designate an opioid-related death; currently there is limited access to literal text on the death certificate. These data contain all deaths regardless of state of residence and state of occurrence, and both can be reported. To access these data, a proposal will be developed and submitted to the CDC Research Data Center for approval. After approval, analyses are done on site at a CDC Research Data Center.

Decedent counts and population- and drug utilization-adjusted rates (both yearly and quarterly) will be presented. Drug utilization-adjusted rates will be calculated for the period July 2010 through the most recent DIM data available. Results will provide national estimates of mortality. Age-specific mortality counts and rates will also be provided; due to disclosure protections, some age-specific data might be suppressed and/or data could be aggregated temporally or geographically for reporting. A sensitivity analysis based on the quality of data reported by states will also be included. Where possible, annual state-level rates and decedent counts will be provided; due to

disclosure protections, some states might be suppressed and/or data could be aggregated temporally or geographically for reporting. All results will be presented at the API level only for buprenorphine and comparators (oxycodone, hydrocodone, methadone).

Concomitant substance analysis for buprenorphine involved deaths will be provided for 3 classes: benzodiazepines, opioids, and alcohol.

### Treatment Episode Dataset (TEDS)

TEDS is a compilation of client-level data routinely collected by the individual state administrative data systems to monitor their substance abuse treatment systems.[viii] Generally, facilities that are required to report to the state substance abuse agency (SSA) are those that receive public funds and/or are licensed or certified by the SSA to provide substance abuse treatment (or are administratively tracked for other reasons). TEDS is an admission-based system and TEDS admissions do not represent individuals. Thus, an individual admitted to treatment twice within a calendar year would be counted as two admissions. TEDS does not include all admissions to substance abuse treatment. It includes admissions at facilities that are licensed or certified by a state substance abuse agency to provide substance abuse treatment (or are administratively tracked for other reasons). In general, facilities reporting TEDS data are those that receive state alcohol and/or drug agency funds (including federal block grant funds) for the provision of alcohol and/or drug treatment services.

TEDS collects data on primary, secondary, and tertiary substance problems. Prescription opioids comprise the category: Other opiates and synthetics— and includes buprenorphine, codeine, hydrocodone, hydromorphone, meperidine, morphine, opium, oxycodone, pentazocine, propoxyphene, tramadol and any other drug with morphine-like effects. Substance problems are further defined in the item detailed drug code, which includes specific opioids such as hydrocodone, oxycodone and buprenorphine. Only about half of the states collect information on detailed drug code and while selected information is available in national reports, it is not available in TEDS publicly-available data sets.

**Objective**

- To describe counts and percentages of admissions including buprenorphine as the primary, secondary, or tertiary drug of abuse.

**Buprenorphine Categorization**

- Buprenorphine (API)

**Comparators (as captured in TEDS Annual Reports)**

- Any opiates
- Oxycodone (Oxycontin, Percocet)
- Hydrocodone (Vicodin)
- Hydromorphone (Dilaudid)
- Non-prescription methadone
- Other opiates or synthetics
- Heroin
- Alcohol and Other illicit drugs
  - Alcohol
  - Marijuana/hashish
  - Cocaine
    - Crack
    - Other Cocaine
  - Stimulants
    - Methamphetamines/speed
  - Tranquilizers
    - Alprazolam (Xanax)
    - Other benzodiazepines
  - Sedatives

**Analysis**

- All treatment admission data will be obtained from published Annual Reports. Data for all years in which they are available will be provided as well as for other drugs of abuse for context including alcohol and illicit drugs. References to any tables used will be included. For all tables and figures, the total number of admissions for each data point will be included where applicable. Possible explanations for the notable increase in abuse reports for buprenorphine between 2014 and 2016 will be provided.

### Abuse and Misuse of Buprenorphine by Adolescents and Young Adults

NSDUH data will be utilized to characterize abuse and misuse in adolescent (12- 17 years of age) and young adult (18 to 25 years of age) populations using the same methodology described previously (Section 4.2.5).

Additional data sources that characterize abuse and misuse in adolescent and young adult populations will be explored and included if available.

### *National Survey on Drug Use and Health (NSDUH)*

**Objective**

- To describe buprenorphine, use and misuse among adolescents (12-17 years of age) and young adults (18-25 years of age), including reasons for misuse. Results will be stratified by Opioid Use Disorder.

**Analysis**

- NSDUH data will be obtained from published annual reports and public use datasets available on or before the end of the applicable SUBOXONE/SUBUTEX REMS Assessment Report reporting period. The prevalence of use and misuse of buprenorphine (API) and comparators among adolescents and young adults will be obtained from published annual reports. Prevalence of misuse among adolescents and young adults will be stratified by Opioid Use Disorder using public use data files. The reason for misuse of specific buprenorphine products (e.g., SUBOXONE) among adolescents and young adults will be obtained from public use data files and will be presented overall and stratified by presence of Opioid Use Disorder. References to any tables used will be included. For all tables and figures, the total number of individuals for each data point will be included where applicable.

### Knowledge, Attitudes, and Behavior (KAB) Surveys of Patients/Caregivers, Pharmacists and Prescribers

The KAB surveys will be conducted with a random sample of patients receiving treatment from office-based prescribers and drug abuse treatment programs in order to assess their awareness and understanding of the risks of SUBOXONE sublingual film as described in the Medication Guide. The surveys will also measure compliance with distribution of the Medication Guide.

The KAB cross-sectional surveys are designed to evaluate the knowledge, attitudes and behavior about the safe use of SUBOXONE sublingual film. The survey will use a standard questionnaire-based design and will be available via telephone and Internet so that participants can choose their preferred method of survey administration. The Electronic Data Capture (EDC) system to be used will be the same for both methods of survey administration and will be validated and secure for receiving and storing survey data. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Respondent identifying information will be stored separately from survey data.

The KAB surveys will be conducted using a questionnaire to document the level of knowledge and assess attitudes and behaviors of patients/caregivers, Pharmacists and Prescribers around the following key risk messages of the REMS:

- The serious risks of accidental overdose, misuse and abuse.
- The importance of appropriate use of buprenorphine products for the treatment of opioid dependence.
- The importance of adhering to the conditions of safe use.
- The importance of safe storage of medication.
- The need for receiving the psychosocial support necessary for safe and effective treatment.
- The need for guarding against unintentional pediatric exposure.

The survey will be repeated prior to each assessment time point. The KAB Protocols and survey questionnaires reflect all FDA comments received to date. The protocols include:

- The expected sample size and confidence intervals associated with that sample size.
- A description of the methodology for recruitment and selection of the patient and prescriber samples.
- The specific selection criteria for inclusion in each survey.
- A description of how and when the surveys will be administered.
- An explanation of the design features and controls that will be included to minimize bias and compensate for any limitations in the methodology.

Draft KAB survey protocols will be submitted to FDA at least 90 days before conducting the surveys.

### *KAB Surveys of Patients/Caregivers*

The KAB surveys of Patients/Caregivers will be conducted among patients who will be recruited through a direct letter program. Patients will be invited through either a national pharmacy chain network partner and/or pharmacy benefits management (PBM) partner, which both have broad demographic coverage. Given that the pool of eligible patients is becoming smaller each year and due to the modifications to the survey, those who participated in the survey in previous waves will be eligible for participation.

### *KAB Surveys of Prescribers*

The KAB survey of Prescribers will be conducted among HCPs who have been informed about the REMS. A list of all DATA 2000-waivered HCPs (including NPs and PAs) who have prescribed SUBOXONE sublingual film to at least one patient in the last 12 months and have not been de-barred or otherwise sanctioned will be generated. The list will contain both low and high prescribers of SUBOXONE sublingual film. A random sample of prescribers from this list will be invited to participate via an Invitation Letter. Given that the pool of eligible prescribers is becoming smaller each year and due to the modifications to the survey, those who participated in the survey in previous waves will be eligible for participation.

The survey will include a series of multiple-choice, open-ended and closed-ended questions (the majority of which use “true/false” or “yes/no” dichotomous response options). These types of questions will be used to determine current knowledge, attitudes, and behavior regarding prescriber understanding of the risks associated with the use of SUBOXONE sublingual film and the steps being instituted to mitigate those risks.

### *KAB Surveys of Pharmacists*

The KAB surveys for Pharmacists will be conducted among registered pharmacists working in retail pharmacies who dispensed SUBOXONE sublingual film for one or more patients at least once in the past year. A list of retail pharmacies that have ordered, in the past 12 months, SUBOXONE sublingual film from a wholesaler that is contracted with Indivior to purchase SUBOXONE sublingual film and provide their sales data, as available, will be generated. From this list a random sample of pharmacies will be identified for contact. An Introductory Letter will be sent to the pharmacist in charge at each pharmacy. Each Introductory Letter will contain 1 Invitation Letter. The pharmacist in charge will be asked to distribute the Invitation Letter to 1 pharmacist at his/her facility that has dispensed SUBOXONE sublingual film at least once in the past year for one or more patients. Pharmacists who participated in previous survey waves will not be eligible for participation.

## Drug Utilization

**Objective**
To describe utilization of buprenorphine for the treatment of opioid use disorder.

**Study Design**
A retrospective cohort study of patients initiating buprenorphine treatment during a 5-year study period, overall and stratified by calendar year.

**Data Source**
One or more data source that captures longitudinal patient data (commercial insurance, Medicare, Medicaid, no insurance [i.e., cash payment out of pocket]). The patient proportion of each insurance type will be included.

**Cohorts**
The study will utilize up to 2 potential patient cohorts based on insurance coverage/available data:

1. Pharmacy cohort: Patients with a new buprenorphine prescription ("index prescription") and 9 months of pharmacy benefits (or pharmacy data) - 3 months before and 6 months after the index prescription date (available for commercial insurance, Medicare, Medicaid, and cash payments)

2. Pharmacy + medical cohort: Patients with a new buprenorphine prescription ("index prescription") and 9 months of both pharmacy and medical benefits - 3 months before and 6 months after the index prescription date (available for commercial insurance, Medicare, and Medicaid)

New use of buprenorphine will be defined as patients with at least 3 months preceding the index prescription without prior prescriptions for any included buprenorphine products. Patients will be eligible to re-enter the cohort through the study period for all qualifying index prescriptions.

The primary exposure is an aggregate category of the following buprenorphine products/product categories:

- SUBOXONE sublingual film
- Other combination buprenorphine/naloxone sublingual film (e.g., Bunavail®, generics)
- Combination buprenorphine/naloxone sublingual tablets (e.g., Zubsolv®, generics)
- Single-ingredient buprenorphine sublingual tablets

Some exploratory analyses will also explore product-specific information using the 4 categories described above.

**Variables**

Pharmacy cohort:

- Patient Characteristics
  - Age
  - Gender
  - Insurance type (commercial, Medicare, Medicaid, cash)
- Buprenorphine Utilization
  - Index prescription type (i.e., SUBOXONE film, other combination film, combination tablets, or single-ingredient tablets)
  - Number of prescriptions filled
  - Days' supply
  - Daily dose
  - Dose changes (% of patients with increase/decrease)
  - Insurance type/prescription payment type (commercial, Medicare, Medicaid, cash)
  - Post-index switching from one buprenorphine category to another – e.g., number (%) of patients in each index group filling subsequent prescriptions for products in the same or other buprenorphine categories post-index [exploratory]
- Other Prescription Utilization
  - Top 10 other medications filled
    - Details on timing relative to buprenorphine therapy and/or the index buprenorphine claim will be described.
    - Detailed information about medications included in the Top 10 other medications will be provided (e.g., medications included in a medication class category, such as "Specific Antagonists" or "Codeine and Combinations", will be described)
    - For the category of "Seizure Disorders", information by drug (e.g., gabapentin, pregabalin, phenytoin) will be provided
  - Concomitant use (chronic/acute) of:
    - Benzodiazepines
    - Opioid analgesics

Pharmacy + medical cohort

All variables described for the pharmacy cohort, plus:

- Health Care System Utilization
  - Treating physician, by specialty
  - Number (%) of patients with office visits for drug dependency
  - Number of office visits for drug dependency

- Number (%) of patients receiving counseling
- Number (%) of patients with labs of interest (labs for alcohol, tobacco, narcotic, controlled substances, or illicit substances)
- Number of labs of interest per patient

All calculations (e.g., formula for calculating means days' supply and mean daily dose) will be described in the final report. All drug codes, procedure codes, and/or diagnostic codes used in the analysis will also be described.

**Statistical Analysis**
All analyses will be descriptive, including frequency and percentage for categorical/dichotomous variables and mean, standard deviation, median, and interquartile range for continuous variables. All results will be presented in tabular format.

All analysis will examine patients by stage of treatment: Month 1 vs. Month 2-6. Some variables (e.g., days' supply) will also be described for the index prescription.

### *Intervention Strategies*

Indivior has established strategies to address the need to minimize the potential for diversion of its buprenorphine products. The current strategies described below will be incorporated into the REMS assessment process.

#### Prescriber Non-compliance

Indivior will routinely monitor prescribing behavior to identify noncompliance. This includes a comparison of DATA 2000-waivered prescribers against current prescribers identified from prescription data sources and product PI recommendations.

#### Other Interventions

Indivior has personnel who are responsible for overseeing the direction, planning, execution and interpretation of its risk management activities used for evaluating and mitigating the diversion of SUBOXONE sublingual film, Authorized Generic of SUBOXONE sublingual film, SUBOXONE sublingual tablet, and SUBUTEX sublingual tablet under the direction of Indivior's medical department.

Another potential source of diversion of buprenorphine containing products is through inappropriate prescribing by practitioners. Indivior will continue its process for Clinical Specialists and other field staff to report any concerns they have that a practitioner appears to be inappropriately prescribing. Based upon validation of the information received and additional data obtained by Indivior's risk management program staff, a plan to intervene will be established. Efforts will be made to inform the prescriber on the

importance of adhering to and documenting the elements listed in the Appropriate Use Checklist, specifically, proper patient selection; discussing the Medication Guide and safe storage conditions with the patient; to dose the medication appropriately and to provide a limited amount of medication at the first visit; and the need for counseling and monitoring progress toward treatment goals. When deemed necessary, Indivior will notify the appropriate state licensing board.

As deemed necessary by REMS surveillance activities, a publication entitled *Medical Advisory & Best-Practices Update* will be mailed to all DATA 2000-waivered HCPs.

Indivior may provide unrestricted educational grants to third parties to fund continuing medical education related to the treatment of opioid dependence.

### Expert Advisory Group

Indivior is a subscriber to the RADARS System and as such, interacts with and utilizes the services of RADARS' staff and its group of external advisors. Indivior personnel may meet with RADARS staff and the expert advisors on an annual basis and as otherwise requested.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.
We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 020732 REMS ASSESSMENT METHODOLOGY**
**NDA 020733 REMS ASSESSMENT METHODOLOGY**
**NDA 022410 REMS ASSESSMENT METHODOLOGY**

An authorized generic drug under these NDAs must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under one or more of these NDAs, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 020732 REMS ASSESSMENT**
**NDA 020733 REMS ASSESSMENT**
**NDA 022410 REMS ASSESSMENT**

***or***

**NEW SUPPLEMENT FOR**
**NDA 020732/S-000**
**NDA 020733/S-000**
**NDA 022410/S-000**
**CHANGES BEING EFFECTED IN 30 DAYS**
**PROPOSED MINOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR**
**NDA 020732/S-000**
**NDA 020733/S-000**
**NDA 022410/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED MAJOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR**
**NDA 020732/S-000**
**NDA 020733/S-000**
**NDA 022410/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX**

***or***

**NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR**
**NDA 020732/S-000**
**NDA 020733/S-000**
**NDA 022410/S-000**
**REMS ASSESSMENT**
**PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

**REMS REVISIONS FOR 020732, NDA 020733, NDA 022410**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

## SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

## REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at 301-796-4085.

Sincerely,

*{See appended electronic signature page}*

Judith A. Racoosin, MD, MPH
Deputy Director for Safety
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- REMS

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[i] RADARS System. RADARS System Programs. https://www radars.org/radars-system-programs html. Accessed September 18, 2019.
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[iii] RADARS System. RADARS System Programs Opioid Treatment. https://www.radars.org/radars-system-programs/opioid-treatment.html. Accessed September 18, 2019.
[iv] RADARS System. RADARS System Programs Survey of Key Informants' Patients. https://www.radars.org/radars-system-programs/survey-of-key-informants-patients html. Accessed September 18, 2019.
[v] RADARS System. RADARS System Programs Drug Diversion. https://www.radars.org/radars-system-programs/drug-diversion.html. Accessed September 18, 2019.
[vi] Drug Enforcement Administration, Diversion Control Division, National Forensic Laboratory Information Systems. NFLIS-Drug 2017 Annual Report. https://www.nflis.deadiversion.usdoj.gov/Reports.aspx. Accessed September 18, 2019.
[vii] Substance Abuse and Mental Health Data Archive (2019). National Survey of Substance Abuse Treatment Services (N-SSATS). https://www.datafiles.samhsa.gov/study-series/national-survey-substance-abuse-treatment-services-n-ssats-nid13519. Accessed September 18, 2019.
[viii] Substance Abuse and Mental Health Services Administration. Treatment Episode Dataset. https://www.samhsa.gov/data/data-we-collect/teds-treatment-episode-data-set. Accessed September 19, 2019.

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

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/s/

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JUDITH A RACOOSIN
03/02/2020 05:35:04 PM