



NDA 209819

**NDA APPROVAL**

Indivior Inc.  
Suite 430  
10710 Midlothian Turnpike  
Richmond, VA 23235

Attention: Clorey Toombs  
Director, Regulatory Global Development

Dear Ms. Toombs:

Please refer to your New Drug Application (NDA) dated and received May 30, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SUBLOCADE (buprenorphine extended-release) injection for subcutaneous use, 100 and 300 mg.

This new drug application provides for the use of SUBLOCADE for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

### **WAIVER OF HIGHLIGHTS SECTION**

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 209819.**” Approval of this submission by FDA is not required before the labeling is used.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected risk of serious fertility, embryo-fetal developmental, and/or pre-/post-natal developmental adverse events, or cancer due to chronic exposure to the excipient N-methyl-pyrrolidone.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

- 3308-1 Conduct a fertility and early embryonic development study testing N-methyl-pyrrolidone in the rat model.

The timetable you submitted on November 30, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 02/2018  
Final Protocol Submission: 04/2018  
Study Completion: 11/2018  
Final Report Submission: 03/2019

- 3308-2 Conduct an embryofetal development study testing N-methyl-pyrrolidone in the rat model.

The timetable you submitted on November 30, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 02/2018  
Final Protocol Submission: 04/2018  
Study Completion: 09/2018  
Final Report Submission: 02/2019

- 3308-3 Conduct an embryofetal development study testing N-methyl-pyrrolidone in the rabbit model.

The timetable you submitted on November 30, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 02/2018  
Final Protocol Submission: 04/2018  
Study Completion: 09/2018  
Final Report Submission: 02/2019

- 3308-4 Conduct a pre- and post-natal development study testing N-methyl-pyrrolidone in the rat model.

The timetable you submitted on November 30, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 03/2018  
Final Protocol Submission: 05/2018  
Study Completion: 09/2018  
Final Report Submission: 05/2019

- 3308-5 Conduct a mode of action (MOA) assessment for N-methyl-pyrrolidone (NMP)-induced mouse hepatocellular adenomas and carcinomas to inform the human risk assessment for NMP.

The timetable you submitted on November 30, 2017, states that you will conduct this study according to the following schedule:

Draft MOA Assessment Submission:	02/2018
Final MOA Assessment Submission:	06/2018
Final MOA Assessment Submission with in vitro study data if deemed necessary:	11/2018

In the clinical trial conducted as part of the development program for SUBLOCADE, some dose-dependent adverse events were noted, while dose-dependent incremental efficacy was not demonstrated for the study population as a whole. However, some subset analyses suggested that there could be sub-populations (e.g., intravenous drug abusers) who may benefit from the higher dose regimen. Identifying these subpopulations, and providing patient selection guidance to clinicians on when the risks of the higher dose regimen are likely to be outweighed by benefits, would contribute to safer use of the drug, including decreasing the risk of serious dose-related adverse events such as hepatotoxicity.

Additionally, the clinical trial was conducted in patients who initiated treatment with sublingual buprenorphine/naloxone (SL BPN), and then tolerated and completed an initial open-label run-in with SL BPN. In the current medical climate, there is great interest in initiating treatment using a depot formulation as rapidly as possible, increasing the likelihood of the patient adherence to treatment from the outset, and reducing the need to provide take-home SL BPN medication for outpatient use. It is, therefore, anticipated that clinicians may elect to accelerate the initiation of SUBLOCADE treatment by omitting some or all of the SL BPN titration period. However, because the doses of buprenorphine provided by SUBLOCADE are higher than doses of SL BPN typically used to initiate treatment, there is a risk that precipitated withdrawal, a clinically serious condition, could occur if SUBLOCADE is initiated without a period of SL BPN titration. Further information on how SUBLOCADE could be initiated without SL BPN titration would contribute to safer use of the drug.

We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the following known serious risks:

- Dose-related toxicity (e.g., elevated liver function tests) that may occur in patients who would be adequately treated at lower doses
- Precipitated withdrawal in patients treated with SUBLOCADE without initial SL BPN titration.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

- 3308-6 Conduct a postmarketing clinical trial comparing two dosing regimens of SUBLOCADE (300 mg/month x 2 months (loading dose) followed by either 300 mg/month or 100 mg/month maintenance doses) in patients who are predicted to benefit from the higher dosing regimen. The population should be selected based on analysis of possible predictors of benefit in Study RB-US-13-0001, including, but not limited to, historical pattern of drug use, addiction severity, or other factors. The goal of the trial is to identify the population of patients for whom the benefits of the 300 mg per month maintenance regimen outweigh the risks of the higher maintenance dose (i.e., clinically meaningful adverse events like hepatotoxicity).

The timetable you submitted on November 30, 2017, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	05/2018
Final Protocol Submission:	03/2019
Trial Completion:	03/2021
Final Report Submission:	08/2021

- 3308-7 Conduct a postmarketing clinical trial exploring how SUBLOCADE can be safely initiated without a period of sublingual buprenorphine (SL BPN) titration. The goals of the trial are to determine a tolerable dose-initiation regimen using SUBLOCADE and assess the associated risk of precipitated withdrawal. Prespecify the case definition of precipitated withdrawal/lack of tolerability for the purposes of quantifying the risks of a more rapid initiation of SUBLOCADE.

The timetable you submitted on November 30, 2017, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	05/2018
Final Protocol Submission:	03/2019
Trial Completion:	03/2021
Final Report Submission:	08/2021

Submit clinical protocol(s) to your IND 107607 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically

report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

### **POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

The clinical pharmacology modeling suggests that SUBLOCADE might be effective when given at dosing intervals less frequent than monthly. Less frequent injections would contribute to less accumulation of the drug, fewer injection site reactions, as well as potentially increase adherence to treatment.

SUBLOCADE was studied only in patients new to treatment, and the dosing regimen was designed to rapidly achieve a blocking dose, which is considered important in extinguishing illicit drug self-administration. However, SUBLOCADE may also be useful in patients who are already clinically stable and abstinent after a period of treatment with transmucosal buprenorphine. Such patients, particularly those stable on doses of 12 mg/day or below, may not require the loading dose or the plasma exposures delivered by the recommended regimen.

We remind you of your postmarketing commitments:

- 3308-8 Conduct an analysis of previously collected pharmacokinetic (PK) data to compare the safety and efficacy of SUBLOCADE given monthly to SUBLOCADE given at a longer inter-dose interval. PK data have suggested that there is accumulation of SUBLOCADE over time, and that some patients may be adequately treated at a longer interval which may reduce patient burden and improve adherence.

The timetable you submitted on November 30, 2017, states that you will provide this assessment according to the following schedule:

Assessment Submission: 05/2018

- 3308-9 If the analysis of pharmacokinetic data does not successfully address the safety and efficacy of SUBLOCADE given at a dosing interval longer than monthly, conduct a study to compare the safety and efficacy of SUBLOCADE given

monthly to SUBLOCADE given at a longer inter-dose interval. The studied interval should be determined by PK modeling and prediction of the duration of clinically-effective plasma levels.

The timetable you submitted on November 30, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2018
Final Protocol Submission:	05/2019
Study Completion:	07/2021
Final Report Submission:	12/2021

3308-10 Conduct a pharmacokinetic (PK) analysis to evaluate the transition of patients with long term stability on a transmucosal buprenorphine dose to a monthly dose of SUBLOCADE without the use of a loading dose. Establish the cutoff dose for which patients may be converted to 100 mg monthly vs. 300 mg monthly.

The timetable you submitted on November 30, 2017, states that you will conduct this analysis study according to the following schedule:

Assessment Submission:	05/2018
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Submit clinical protocols to your IND 107607 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,”** or **“Postmarketing Commitment Correspondence.”**

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for SUBLOCADE to ensure the benefits of the drug outweigh the risk of serious harm or death with intravenous self-administration.

Your proposed REMS must also include the following:

**Elements to assure safe use:** Pursuant to 505-1(f)(1), we have determined that SUBLOCADE can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of serious harm or death with intravenous self-administration listed in the labeling. The elements to assure safe use will require healthcare settings and pharmacies that dispense SUBLOCADE to be certified to ensure SUBLOCADE is only dispensed directly to a health care provider for administration by a health care provider.

Your REMS includes the following elements to mitigate this risk:

- Pharmacies and healthcare settings that dispense the drug are specially certified

**Implementation System:** The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies and healthcare settings that dispense the drug be specially certified.

Your proposed REMS, submitted on May 30, 2017, amended, and appended to this letter, is approved. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce SUBLOCADE into interstate commerce.

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

1. REMS Operations and Utilization

- a. Number of certified entities; provide for the current reporting period and cumulatively
  - i. healthcare settings that dispense SUBLOCADE
  - ii. pharmacies that dispense SUBLOCADE
- b. Number of wholesalers/ distributors shipping SUBLOCADE; provide for the reporting period and cumulatively
- c. Call Center Report
  - i. Number of contacts
  - ii. Summary of reason for call (Examples include “enrollment question, location of certified healthcare setting, etc.”) by reporter (prescriber, authorized representative, healthcare setting, pharmacy, patient/caregiver, other)

2. REMS Compliance

- a. Number of audits of certified healthcare settings, pharmacies and wholesalers/ distributors or other audits conducted during the reporting period
    - i. Provide the number of expected audits and the number of actual audits conducted, reasons why expected audits weren't conducted, and plan to audit these entities
    - ii. Number of de-certified pharmacies and wholesalers/ distributors resulting from audit findings
    - iii. Summary of all corrective actions and any resulting preventative actions resulting from audit findings for each non-compliant entity
  - b. Number of shipments of SUBLOCADE to non-certified healthcare settings or pharmacies, or other locations (e.g., patient's home) source of report, and corrective actions to prevent shipment to non-certified settings and pharmacies.
    - i. Disposition of SUBLOCADE shipped to non-certified healthcare settings and pharmacies (e.g., drug returned, drug administered)
  - c. Number of non-DATA waived healthcare providers ordering or prescribing SUBLOCADE, source of report (e.g., audit, call center, self-report) number of orders written per non-DATA waived healthcare providers, and resulting corrective actions
  - d. Any other SUBLOCADE REMS non-compliance, source of report and resulting corrective actions
3. Safety surveillance
- a. Provide for reporting period and cumulative analyses of all cases of:
    - i. Known or suspected intravenous administration of SUBLOCADE, regardless of outcome and root cause analyses of what REMS processes were not followed and allowed for intravenous administration with sources including, but not limited to:
      1. Adverse event reports
      2. Literature search
      3. Internet surveillance

With the analyses, provide a case line listing, overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication

- ii. Serious adverse events related to thromboembolic disorders reported with SUBLOCADE. With the analyses, provide a case line listing, overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication
- iii. Known or suspected abuse, misuse, and overdose of SUBLOCADE, regardless of outcome with sources including, but not limited to:
  1. Adverse event reports
  2. Literature search
  3. Internet surveillance

With the analyses, provide a case line listing, overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication.

4. REMS Outreach and communication
  - a. Number, dates, and means of delivery for the letters sent (and packets, as appropriate)
  - b. Name of professional societies receiving REMS letters or other materials
  - c. Source of the list of prescribers, pharmacists, professional societies, pharmacies, wholesalers/distributors, hospitals, closed health system, out-patient clinics, long-term care facilities, Department of Defense facilities, prisons, inpatient psychiatric units, and Opioid Treatment Programs
5. For the 6-month assessment, only:
  - a. Date of first commercial distribution of SUBLOCADE
  - b. Date website live
  - c. Date first health care setting or pharmacy became certified
6. 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). 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, proposed 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 the 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 a REMS modification, 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 209819 REMS CORRESPONDENCE  
(insert concise description of content in bold capital letters, e.g.,  
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT  
METHODOLOGY**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, 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 209819 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 209819/S-000  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 209819/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 209819/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES  
SUBMITTED IN SUPPLEMENT XXX**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 209819/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 REVISION FOR NDA 209819**

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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

**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 [REMS\\_Website@fda.hhs.gov](mailto:REMS_Website@fda.hhs.gov).

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/Guidance/ComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the

form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **EXPIRATION DATING**

The drug product is granted an expiry dating of 18 months when stored at 2°C to 8°C (35.6°F to 46.4°F).

### **REPORTING REQUIREMENTS**

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

To ensure effective surveillance and expeditious review of adverse event reports, perform enhanced pharmacovigilance for a period of 3 years from the date of this letter. The primary enhancements to the current routine pharmacovigilance paradigm are the following:

1. Submit as expedited (15-day) reports all initial and follow-up reports of:
  - a. known or suspected intravenous administration of SUBLOCADE, regardless of outcome (serious or non-serious) and whether the product was self-administered or involved inadvertent intravenous administration by a healthcare provider
  - b. surgical removal of the SUBLOCADE depot and any post-removal complications
  
2. With each periodic safety report submission, include interval and cumulative detailed analyses of the adverse event reports in your postmarket safety database and the medical literature for the following:
  - a. known or suspected intravenous administration of SUBLOCADE, regardless of outcome (serious or non-serious) and whether the product was self-administered or involved inadvertent intravenous administration by a healthcare provider
  - b. serious adverse events related to thromboembolic disorders
  - c. surgical removal of the SUBLOCADE depot and any post-removal complications

With the analyses, provide a case line listing, overall summary, and discussion of whether the data warrants further detailed assessment or regulatory action.

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

Sincerely,

*{See appended electronic signature page}*

Sharon Hertz, MD  
Director  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling  
Carton and Container Labeling  
REMS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHARON H HERTZ  
11/30/2017