DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA ######

RELEASE FROM POSTMARKETING REQUIREMENT
NEW POSTMARKETING REQUIREMENT

COMPANY NAME
ADDRESS 1
ADDRESS 2
CITY, ST ZIP CODE

Attention: COMPANY POINT OF CONTACT
TITLE

Dear COMPANY POINT OF CONTACT:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TRADENAME (established name).

RELEASE FROM POSTMARKETING REQUIREMENT

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 (section 505(o)(3)(A)). FDA previously determined that you were required to conduct the following postmarketing studies listed in our DATE, approval letter:

####-#(a) In order to provide the baseline data to support the hypothesis-testing studies required under PMR ####-#(b), conduct a descriptive study that analyzes data on the following:

(1) utilization of TRADENAME and selected comparators. Reports should include nationally-projected quarterly retail dispensing, overall and by age group and census region;

AND

(2) abuse of TRADENAME and related clinical outcomes. These studies should utilize multiple data sources in different populations to establish the scope and patterns of abuse for TRADENAME as well as mutually agreed-upon, selected comparators to provide context.

- Data should include route-specific abuse outcomes, be nationally-representative or from multiple large geographic areas, and use meaningful measures of abuse.

- Additional information, either qualitative or quantitative, from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies may also be included to help better understand abuse of this drug, including routes and patterns of abuse in various populations.

- Formal hypothesis testing is not necessary during this phase, but provide information on the precision of abuse-related outcome estimates (e.g. 95% confidence intervals for quarterly estimates) and calculate utilization-adjusted outcome estimates where possible.

This study will be conducted according to the following schedule:

Draft Protocol Submission:	MM/YYYY
Final Protocol Submission:	MM/YYYY
Study Completion:	MM/YYYY
Final Report Submission:	MM/YYYY

xxxx-x(b) Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of TRADENAME actually result in a meaningful decrease in misuse and abuse, and their related clinical outcomes, addiction, overdose, and death, in post-approval settings. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of TRADENAME and should incorporate recommendations contained in *Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry* (April 2015). Assessing the impact of the abuse-deterrent formulation on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA's *Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*.

This study will be conducted according to the following schedule:

Draft Protocol Submission:	MM/YYYY
Final Protocol Submission:	MM/YYYY
Study Completion:	MM/YYYY
Final Report Submission:	MM/YYYY

Since the above PMRs were issued at the time of TRADENAME approval on DATE, FDA has observed that there is substantial variability in the time necessary for an opioid product with abuse deterrent properties to have adequate uptake in the market to support the hypothesis testing necessary to determine whether the abuse-deterrent qualities of the formulation actually result in a significant and meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the post-approval setting. Therefore at this time, we are releasing the above PMRs and replacing them with a PMR that will be conducted according to the milestones

listed below. Additionally, we intend to require a second PMR to be conducted following satisfactory completion of the first. FDA is replacing the original PMRs because we have determined that a sequential approach will be more responsive to the uncertainties inherent to this situation- namely, a study that is dependent on adequate uptake of the product in the market.

Therefore, the above postmarketing requirements will be replaced by the new postmarketing requirements with revised milestones as described below:

POSTMARKETING REQUIREMENTS UNDER 505(o)

As you were previously notified in our DATE, letter, 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 assess the known serious risks of misuse and abuse, and their consequences, addiction, overdose, and death.

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 this serious risk. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

####-#(c) Conduct a descriptive study to collect meaningful baseline data to support subsequent formal epidemiologic assessments of the abuse deterrence of TRADENAME. The descriptive study should include data on the following:

1) Utilization of TRADENAME and selected comparators. Reports should include nationally-projected quarterly dispensing data, overall and by age group and census region;

   AND

2) Abuse of TRADENAME and related clinical outcomes. These assessments should utilize multiple data sources in different populations to establish the scope and patterns of abuse for TRADENAME as well as mutually agreed-upon, selected comparators to provide context.

   - Data should include route-specific abuse outcomes, be nationally-representative or from multiple large geographic areas, and use meaningful measures of abuse.

Additional information, either qualitative or quantitative, from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies may also be included to help better understand abuse of this drug, including routes and patterns of abuse in various populations.

Formal hypothesis testing is not necessary during this phase, but provide information on the precision of abuse-related outcome estimates (e.g., 95%

confidence intervals for quarterly estimates) and calculate utilization-adjusted outcome estimates where possible.

This study will be conducted according to the following schedule:

Draft Protocol Submission:	MM/YYYY
Draft Statistical Analysis Plan Submission:	MM/YYYY
Final Protocol Submission:	MM/YYYY
Final Statistical Analysis Plan Submission:	MM/YYYY
Interim Report #1:	MM/YYYY
Interim Report #2:	MM/YYYY
Study Completion:	MM/YYYY
Final Report Submission:	MM/YYYY

In addition, as described in our in our DATE, letter, and following satisfactory completion of PMR ####-#(c), FDA intends to require that you conduct the following:

Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of TRADENAME actually result in a meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the post-approval setting. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of TRADENAME and should incorporate recommendations contained in guidance for industry: *Abuse-Deterrent Opioids—Evaluation and Labeling,* available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm334743.pdf. Assessing the impact of the formulation with abuse deterrent properties on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA's guidance for industry and FDA staff: *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*, available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm243537.pdf.

Additional specific details of this postmarketing requirement, including a timetable and annual reporting requirements, will be described more fully after completion of and review of data for PMR ####-#(c).

Submit the study protocol(s) to your IND #######, with a cross-reference letter to this NDA. Submit 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)"**.

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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.

In addition to the Interim Reports due on the dates listed above for PMR ####-#(c), 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.

If you have any questions, call Mark Liberatore, PharmD, Safety Regulatory Project Manager, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, MD, MPH
Deputy Director for Safety
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research