DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA ######

RELEASE FROM POSTMARKETING REQUIREMENT
NEW POSTMARKETING REQUIREMENT

APPLICANT NAME
ADDRESS
CITY, ST, ZIP

Attention: CONTACT NAME
TITLE

Dear CONTACT:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TRADE NAME (ESTABLISHED NAME) DOSAGE FORM.

RELEASE FROM POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) 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 and clinical trial as detailed in our **[DATE]** approval letters **[OR** postapproval postmarketing requirement letter dated September 10, 2013.**]**

2065-1 Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

These studies should address at a minimum the following specific aims:

a. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.

b. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

The following timetable proposes the schedule by which you will conduct these studies:

Final Protocol Submission:	08/2014
Study Completion:	01/2018
Final Report Submission:	06/2018

2065-2 Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	08/2014
Study Completion:	08/2015
Final Report Submission:	11/2015

2065-3 Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	08/2014
Study Completion:	08/2015
Final Report Submission:	11/2015

2065-4 Conduct a study to define and validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	08/2014
Study Completion:	08/2015
Final Report Submission:	11/2015

2065-5 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission:	08/2014
Trial Completion:	08/2016
Final Report Submission:	02/2017

We have reviewed the submissions from the Opioid PMR Consortium (OPC) providing final protocols for the above listed PMRs. Based on feedback obtained from stakeholders on the design and conduct of the postmarketing requirements[1], at this time we are releasing the above five PMRs and replacing them with the following eleven PMRs (ten postmarketing studies and one clinical trial). FDA is replacing the five original PMRs because the ten postmarketing observational studies and one clinical trial include refined measures for assessing the known serious risks of misuse, abuse, addiction, overdose, and death. The timetables for completion of these PMRs are listed below.

The above postmarketing requirements will be replaced by the new postmarketing requirements as described below:

POSTMARKETING REQUIREMENTS UNDER 505(o)

As you were previously notified, 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, abuse, addiction, hyperalgesia, overdose, and death associated with the long-term use of ER/LA opioid analgesics, of which DRUG is a member.

[1] See, e.g., Postmarketing Requirements for the Class-Wide Extended-Release/ Long-Acting Opioid Analgesics; Public Meeting; Request for Comments, available at http://www.regulations.gov/#!docketDetail;D=FDA-2014-N-0374 (regarding public meeting held May 19 and 20, 2014).

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:

3033-1 A prospective, observational study designed to quantify the serious risks of misuse, abuse, and addiction associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics.

This study must address at a minimum the following specific objectives:

a. Estimate the incidence of misuse, abuse, and addiction associated with long-term use of opioid analgesics for chronic pain. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, and addiction.

b. Evaluate and quantify other risk factors for misuse, abuse, and addiction associated with long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	11/2015 (completed)
Interim Report (Cumulative Enrollment of 470 patients)	05/2017
Interim Report (Cumulative Enrollment of 1,042 patients)	09/2017
Interim Report (Cumulative Enrollment of 1,609 patients)	01/2018
Interim Report (Cumulative Enrollment of 2,300 patients)	06/2018
Study Completion:	10/2019
Final Report Submission:	03/2020

3033-2 An observational study designed to measure the incidence and predictors of opioid overdose and death (OOD), as well as opioid abuse/addiction, using patient health records, insurance claims, and death records.

This study must address at a minimum the following specific objectives:

a. Estimate the incidence of abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain. Stratify overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or

family history of substance abuse, history of psychiatric illness) on the risk of abuse/addiction, overdose, and death.

b. Evaluate and quantify other risk factors for abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify overdose by intentionality wherever possible.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	11/2014 (completed)
Study Completion:	04/2019
Final Report Submission:	09/2019

3033-3 A prospective observational study designed to assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Patient understanding of the concepts of misuse and abuse will also be obtained.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	04/2015 (completed)
Study Completion:	10/2015 (completed)
Final Report Submission:	01/2016 (completed)

3033-4 An observational study to evaluate the validity and reproducibility of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term opioid analgesic use.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	04/2015 (completed)
Study Completion:	10/2016
Final Report Submission:	02/2017

3033-5 An observational study to validate measures of prescription opioid Substance Use Disorder and addiction in patients who have received or are receiving opioid analgesics for chronic pain.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	04/2015 (completed)
Study Completion:	12/2016
Final Report Submission:	05/2017

3033-6 An observational study to develop and validate an algorithm using coded medical terminologies and other electronic healthcare data to identify opioid-related overdose and death.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	11/2014 (completed)
Study Completion:	09/2016
Final Report Submission:	12/2016

3033-7 An observational study to develop and validate an algorithm using coded medical terminologies to identify patients experiencing prescription opioid abuse or addiction, among patients receiving an ER/LA opioid analgesic.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	11/2014 (completed)
Study Completion:	10/2016
Final Report Submission:	01/2017

3033-8 An observational study using coded medical terminologies and other electronic healthcare data to define and validate doctor and/or pharmacy shopping outcomes by examining their association with abuse and/or addiction.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	03/2015 (completed)
Study Completion:	10/2017
Final Report Submission:	01/2018

3033-9 An observational study using a validated patient survey to evaluate the association between doctor/pharmacy shopping outcomes and self-reported misuse and abuse.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	03/2015 (completed)
Study Completion:	09/2018
Final Report Submission:	12/2018

3033-10 An observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.

The following timetable is the schedule by which you will conduct this study:

Final Protocol Submission:	03/2015 (completed)
Study Completion:	03/2017
Final Report Submission:	06/2017

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of hyperalgesia associated with the class of ER/LA opioid analgesics, of which DRUG is a member. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3033-11 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain. Include an assessment of risk relative to efficacy.

The following timetable is the schedule by which you will conduct this trial:

Final Protocol Submission:	11/2014 (completed)
Trial Completion:	02/2019
Final Report Submission:	08/2019

We encourage you to work together with the holders of other approved NDA applications for ER/LA opioid analgesics on these studies and clinical trial to provide the best information possible.

Submit the protocol to your IND ######, with a cross-reference letter to your NDA. Submit all final reports 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.

If you have any questions, contact Mark Liberatore, PharmD; Safety Regulatory Project Manager at mark.liberatore@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, M.D., M.P.H.
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