Department of Health and Human Services
Public Health Service
Food and Drug Administration Center for
Drug Evaluation and Research Office of
Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Review of Proposed Methodology and Survey Instruments for the Risk Evaluation and Mitigation Strategy (REMS) Assessment

Date:	January 11, 2013
Reviewer:	Julia Ju, Pharm.D., PhD, Social Science Reviewer Division of Risk Management (DRISK)
Team Leader:	Doris Auth, Pharm.D. DRISK
Associate Director	Mary E. Willy, PhD. DRISK
Drug Name(s):	See table below
Therapeutic Class:	Opioid Agonist: Extended-Release and Long-Acting Opioid Analgesic Drugs

Drug Name	Dosage and Route	Application Type/Number	Applicant\ Sponsor	TSI #
AVINZA (morphine sulfate)	extended-release capsules	NDA 021260	King	466
BUTRANS (buprenorphine)	transdermal system	NDA 021306	Purdue	466 880
DOLOPHINE (methadone hydrochloride)	tablets	NDA 006134	Roxane	466 254
Methadone	oral solution	ANDA 087997	Roxane	--
Methadone	oral solution	ANDA 087393	Roxane	--
Methadone	oral concentrate	ANDA 089897	Roxane	--
DURAGESIC (Fentanyl Transdermal System)	transdermal system	NDA 019813	Ortho-McNeil	466 392 255
EMBEDA (morphine sulfate and naltrexone hydrochloride	extended-release capsules	NDA 022321	Alpharma/King	466 1083 1135

Drug Name	Dosage and Route	Application Type/Number	Applicant\ Sponsor	TSI #
EXALGO (hydromorphone HCl)	extended-release capsules	NDA 021217	Mallinkrodt	466
KADIAN (morphine sulfate)	extended-release capsules	NDA 020616	Actavis	466
MS CONTIN (morphine sulfate)	controlled-release tablets	NDA 019516	Purdue	466
NUCYNTA ER (tapentadol)	extended-release oral tablets	NDA 200533	Ortho-McNeil	466 926
OPANA ER (oxymorphone hydrochloride)	extended-release oral tablets	NDA 201655	Endo	466
OPANA ER (oxymorphone hydrochloride)	extended-release oral tablets	NDA 021610	Endo	466
OXYCONTIN (oxycodone hydrochloride	controlled-release tablets	NDA 020553	Purdue	466 1136
OXYCONTIN (oxycodone hydrochloride	controlled-release tablets	NDA 022272	Purdue	466 1072

INTRODUCTION

This review is in response to a consult request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) for the Division of Risk Management (DRISK) to review the methodology and survey instruments that will be used as a baseline assessment of prescribers' understanding of the appropriate use of extended release/long acting (ER/LA) opioid analgesics prior to the implementation of the single shared REMS-compliant continuing education (CE) programs and the follow-up REMS assessment surveys.

The goals of the baseline survey are to estimate, among prescribers who prescribed an ER/LA opioid analgesic, baseline knowledge about prescribing ER/LA opioids and information on their ER/LA opioid prescribing behavior and practice prior to implementation of the REMS program. This survey will identify prescribers' understanding of proper patient selection, general ER/LA opioid use, the potential risks associated with use of ER/LA opioid analgesics, dosing and administration requirements, and compliance with counseling patients.

Please send the comments provided in this review to the Applicant within two weeks and copy DRISK on the correspondence. Let us know if you would like a meeting to discuss these comments before sending to the Applicant.

1.1 BACKGROUND

ER/LA opioid analgesic medicines are indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The ER/LA opioid analgesics include Avinza, Butrans, Dolophine, Duragesic, Embeda, Exalgo, Kadian, MS Contin, Nucynta ER, Opana ER, Oxycontin ER, Palladone, and generic versions of any of these brands.

1.2 REGULATORY HISTORY

On April 19, 2011, the Food and Drug Administration (FDA) notified manufacturers of ER/LA opioid analgesics that a class-wide, single shared REMS was required. The sponsors of the ER/LA opioid analgesics formed an industry working group called the REMS Program Companies (RPC) to prepare the REMS proposal for FDA approval and to operationalize the REMS program once approved. On July 9, 2012, the single-shared ER/LA opioid analgesics REMS was approved.

The goal of the ER/LA opioid analgesics REMS program is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

REMS elements include a Medication Guide, Elements to Assure Safe Use (ETASU) (training will be made available to healthcare providers who prescribe ER/LA opioid analgesics), and a timetable for submission of assessments of the REMS at 6 months and 12 months after the initial approval date of the REMS, and annually thereafter.

The REMS Assessment Plan includes the followings:

- An assessment of the number of prescribers who have completed REMS-compliant training
- A summary of independent audits of training
- Evaluation of healthcare provider understanding of the training information using surveys
- Evaluation of patient understanding of the safe use of ER/LA opioids using surveys
- Surveillance of abuse, misuse, overdose, addiction, and death from ER/LA opioids
- Evaluation of drug utilization patterns
- Evaluation of prescribing behaviors
- Monitoring patterns of prescribing that suggest changes in patient access to ER/LA opioids.

2 REVIEW MATERIALS AND METHODS

2.1 Material Reviewed

- July 6, 2012, DRISK final REMS review by D. Smith and M. Willy
- July 9, 2012, REMS approval letter
- October 31, 2012, survey protocol entitled "Quantitative Testing of prescriber knowledge, attitude, and behavior about extended-release (ER) and long-acting (LA) opioid analgesic products safety and use information"

2.2 Review Methods

The social scientist reviewed the sponsor's proposed methodology. The review included an evaluation of the sample size, recruitment methods and materials, data collection methods, inclusion criteria and survey instrument, to determine if the proposed methodology is appropriate to effectively assess prescribers' knowledge as outlined in the study objectives of this baseline survey.

3 RESULTS OF REVIEW

3.1 Prescriber Survey Protocol

3.1.1 Study Objectives

The proposed study objectives are:

- To assess the understanding of ER/LA opioid prescribers of the serious risks associated with the use of the ER/LA opioids and how to prescribe ER/LA opioids appropriately, including the five domains of FDA Blueprint.
- To assess ER/LA opioid prescribers' opioid prescribing behavior and practice, including questions from the five domains from the FDA Blueprint, where applicable and feasible.

Reviewer Comments:

The proposed study objectives are appropriate.

3.1.2 Survey Administration Modalities

The survey will be self-administered online through a secure website.

Reviewer Comments:

The proposed survey administration modality is not adequate. Another modality, such as telephone surveys facilitated by a trained interviewer from the survey coordinating center using a computer-assisted telephone interviewing (CATI) program should be added as this will increase the potential for prescriber participation and understanding the potential issues with the survey instruments.

3.1.3 Study Population and Participant Recruitment

This survey will be conducted among a sample of prescribers who have prescribed an ER/LA opioid at least once in the year prior to the survey administration identified via the IMS prescription database by the RPC. A statistician will select a random sample from each formulation group (transdermal patch, methadone, and oral products) stratified by medical specialty (specialists, general practice and primary care physicians, and non-MD prescribers), prescribing level, and geographic regions of the U.S.

If the required number of completed surveys is not achieved within approximately 10 days after the first mailing, a second mail or e-mail will be sent to non-respondents from the original sample with subsequent fax and/or e-mail to maximize participation. If these efforts do not result in the required number of surveys within two to three weeks, then a new sample will be selected.

Reviewer Comments:

The Applicant should consider excluding prescribers whose immediate family members have ever worked for the sponsors of any ER/LA opioid analgesics or the FDA from participating in the surveys to minimize potential bias of survey results.

3.1.4 Sample Size

Based on both practical and statistical considerations, a sample of 600 prescribers is proposed for the baseline survey. A similar sample size is assumed for the post-REMS survey as well. There is no target knowledge rate specified *a priori*. A sample of 600 completed surveys will allow estimation of the knowledge rate for each risk message with a moderately high degree of precision.

Reviewer Comments:

The proposed sample size of 600 prescribers is acceptable.

3.1.5 Qualitative Pre-testing of the Survey

To assess prescriber comprehension and interpretation of the survey questionnaire, cognitive debriefing interviews will be conducted with healthcare providers (HCPs) who have written prescriptions for ER/LA opioid analgesics. A total of 24 HCPs will be recruited for in-depth telephone interviews for approximately 60 minutes. Feedback collected will help to identify terms, questions, and topics for clarification and revision based on areas of confusion and miscomprehension.

Reviewer Comments:

The proposed pre-testing of the survey questionnaire is appropriate.

3.1.6 Survey Process

The survey will begin with screening questions to confirm respondents' eligibility to participate in the survey. All questions will be programmed to ensure that questions are asked in the appropriate sequence. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

Reviewer Comments:

The proposed survey process is appropriate.

3.1.7 Analysis

Questionnaires will be analyzed to determine prescribers' understanding of each key risk message. Descriptive statistics for the survey administration, study population, and the survey questions will be provided. The following will be reported as part of the analysis:

- The number of invitations issued to prescriber
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents who complete the survey
- Representativeness of prescribers based on geography
- Description of survey participants, including:
    - Medical degree of respondent: MD, DO, NP/APN, PA
    - Medical specialty (neurologists, anesthesiologists, rheumatologists, orthopedics, oncologists, hospice/palliative care providers, general practice and primary care physicians)
    - Years of professional experience
    - Number of times ER/LA opioid analgesics were prescribed in the last 12 months
    - Types of ER/LA opioid analgesics prescribed (transdermal patch, methadone, and oral products)
    - Geographic region of practice

The primary analysis for each key risk message evaluates the rate for each correct response to each individual question defined by the key risk message. Secondary analyses are done only for those key risk messages that contain multiple questions/items.

Reviewer Comments:

If possible, the representativeness of prescriber sample should be assessed based on prescribers' medical specialty, medical degree, and geography. The rest of the proposed survey analysis is appropriate.

3.1.8 Survey Instrument

There are a total of 56 questions proposed in this survey. Two (questions 1-2) of them are the screening questions to confirm the eligibility of the participants and six (questions 51-56) of them are questions to capture the survey participants' demographic information. Twenty five questions (questions 3-27) are on the key risk messages of ER/LA opioid analgesics products. Twenty questions (questions 28-47) are about the educational materials for ER/LA opioid analgesics, Medication Guide, Dear DEA-Registered Prescriber Letter, patient counseling document (PCD), and the ER/LA opioid analgesics REMS website. One open-ended question (question 48) on what are the participants' questions, if they have any questions about the information in the Medication Guide, Dear DEA-Registered Prescriber Letter, PCD, or ER/LA opioid REMS website. One question (question 49) was proposed to capture the perceived burden for patients to access to the ER/LA opioid analgesics.

Five key risk messages were identified from the FDA Blueprint for prescriber education for ER/LA opioid analgesics.

1. Patients should be assessed for treatment with ER/LA opioid analgesic therapy.
2. Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
3. Management of ongoing therapy with ER/LA opioid analgesics is important.
4. It is important to counsel patients and caregivers about the safe use of ER/LA opioid analgesics.
5. Prescribers must be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

Reviewer Comments:

The key risk messages identified in this proposal were appropriate. However, additional questions or answer options should be added to the proposed survey questionnaire to assess the prescribers' comprehensive baseline understanding and knowledge of the key risk messages of ER/LA opioid analgesics identified from the FDA's Blueprint. For example, one answer options (8d.) can be added to question #8: "Please select True, False, or I don't know for each of the following statements about drug-drug interaction profiles for ER/LA opioid analgesics.

8a. Central nervous system depressants can have a potentiating effect on the sedation and respiratory depression caused by opioids.
8b. Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol.
8c. Monoamine oxidase inhibitors (MAOIs) are the preferred antidepressants for use with ER/LA opioid analgesics.
8d. Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids."

Errors in the numbering of the proposed survey questions were noticed during this review. On page 63 of the proposal, question #48c should be changed to question #49c. On the same page, question #49 should be changed to #50, and so on for all questions afterwards.

4 CONCLUSIONS AND RECOMMENDATIONS

The proposed survey protocols are generally acceptable except the need for a few modifications. These modifications need to be completed before the launch of the baseline survey. The following comments are for the ER/LA opioid analgesic sponsors.

We acknowledge that you provided the survey methodology and instrument to assess the prescribers' baseline understanding of the key risk messages and safe use conditions of ER/LA opioid analgesics. We offer the following comments and recommendations for the proposed survey protocol. Please modify the survey protocol accordingly before the launch of the baseline survey.

- *Another survey modality, such as telephone surveys facilitated by a trained interviewer from the survey coordinating center using a computer-assisted telephone interviewing (CATI) program should be added to the proposed self-administered internet-based survey modality.*
- *You should exclude prescribers whose immediate family members have ever worked for the sponsors of any ER/LA* opioid analgesics *or the FDA from participating in the surveys to minimize potential bias of survey results*
- *You should report the representativeness of prescriber sample based on their medical specialty, medical degree, and geography, if possible.*
- *You should add additional questions or answer options to assess the prescribers' comprehensive baseline understanding and knowledge of the key risk messages of ER/LA opioid analgesics identified from the FDA's Blueprint. For example, one answer option (8d.) should be added to question #8: "Please select True, False, or I don't know for each of the following statements about drug-drug interaction profiles for ER/LA opioid analgesics.*

  8a. Central nervous system depressants can have a potentiating effect on the sedation and respiratory depression caused by opioids.
  8b. Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol.
  8c. Monoamine oxidase inhibitors (MAOIs) are the preferred antidepressants for use with ER/LA opioid analgesics.
  8d. Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids."
- *You should correct the errors in the numbering of survey questions.*
- *Do not submit your methodology and instrument again prior to the assessment submission. Submit all methodology and instruments utilized with your assessments.*

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/s/

JING JU
01/11/2013

MARY E WILLY
01/11/2013
I concur