

## **Incorporating Continuing Education into Single-Drug REMS: Exploring the Challenges and Opportunities**

May 18, 2015

### **Discussion Guide**

#### **Introduction**

Under Title IX of the Food and Drug Administration Amendments Act of 2007 (FDAAA), the U.S. Food and Drug Administration (FDA) has the authority to require sponsors to develop Risk Evaluation and Mitigation Strategies (REMS) for drugs or biologics that carry serious potential or known risks. The REMS program has become an important tool in ensuring that the benefits of a given medical product outweigh the associated risks, and has enabled the agency to approve a number of products that might not otherwise have been made available for patient use. Since the implementation of the REMS program, however, concerns have been raised regarding its impact on patient access to products and the associated burden on providers and health care systems.<sup>1</sup> In an effort to address these concerns—and as part of its commitments under the Prescription Drug User Fee Act reauthorization of 2012 (PDUFA V)—FDA has undertaken efforts to standardize and improve the effectiveness of REMS, and to better integrate REMS tools into the health system.<sup>2</sup>

Following extensive consultation with a range of stakeholders, in September 2014 the agency outlined four priority projects that it will pursue, one of which focuses on health care provider education under REMS.<sup>3</sup> To this end, FDA is exploring the feasibility of integrating accredited continuing education (CE) programs and activities into REMS that have been developed for a single drug. In support of these efforts, and convened under a cooperative agreement with FDA, the Center for Health Policy at Brookings is hosting this workshop in order to: 1) build upon the lessons learned from the previous CE program for the Extended Release/Long-Acting opioid REMS; 2) define the critical elements that CE should have in order to be a valuable addition to the REMS toolkit; and 3) identify existing barriers to REMS CE development and implementation, as well as potential strategies to overcome them.

#### **Risk Evaluation and Mitigation Strategies (REMS)**

Approved professional labeling is the primary tool that FDA uses to ensure the benefits outweigh the risks of the drugs that it approves for use. Labeling describes the conditions in which the drug can be used safely and effectively, and is updated from time to time to incorporate information from postmarketing surveillance or studies that reveal new benefits (e.g., new indications or formulations) or risk concerns.

However, FDA employs a range of additional tools for products with significant safety concerns. Prior to the passage of FDAAA, a small number of drugs were approved by FDA with a Risk Minimization Action Plan (RiskMAP). RiskMAPs were designed for drugs that required safety measures above and beyond the approved labeling and routine reporting requirements, and included several tools designed to meet specific objectives in minimizing drug risks.<sup>4,5</sup> When FDAAA authorized FDA to require REMS for

prescription drug and biological products in 2007, many of the principles used to develop RiskMAPs informed the development and implementation of REMS.

*Development, Implementation, and Assessment of REMS*

REMS may be required by FDA before a drug is approved, or may be required post-approval if new safety information becomes available that shows a serious risk of adverse events associated with the drug. The process of designing, implementing, and evaluating a REMS program is the responsibility of the drug’s sponsor (i.e., its manufacturer). FDA specifies the required elements of the REMS, and sponsors submit a proposed REMS design for their product. The proposal is then reviewed and adapted in consultation with FDA, which then approves the REMS for implementation. As of May 9, 2015, there were 75 REMS programs for individual drugs and biologic products in place, and six shared system REMS that apply to an entire class of products.<sup>6</sup>

A given REMS program can include one or more elements as well as a diverse set of materials and processes (collectively referred to as ‘tools’) to help mitigate the risks of a particular drug. (See Table 1)

**Table 1: Available REMS Elements**

REMS Element	Definition	Example tool
<b>Medication Guide or Patient Package Insert</b>	Paper handouts that address issues that are specific to particular drugs and drug classes. These handouts contain FDA-approved information that can help patients avoid serious adverse events.	N/A
<b>Communication Plan (CP)</b>	Strategies to inform targeted health care providers and professional societies of the REMS requirements, encourage implementation, and/or explain the serious risks and appropriate safety measures associated with the drug’s use.	<ul style="list-style-type: none"> <li>• Dear Healthcare Provider Letters</li> <li>• Websites</li> <li>• Factsheet</li> <li>• Journal Information Pieces</li> </ul>
<b>Elements to Assure Safe Use (ETASU)</b>	Specific interventions or other actions required by health care providers before they may prescribe or dispense the drug. ETASU may also be necessary throughout a course of treatment of the drug.	<ul style="list-style-type: none"> <li>• Health care providers who prescribe the drug have specific training or experience or are specially certified;</li> <li>• Pharmacies, practitioners, or health care settings that dispense the drug are specially certified;</li> <li>• Drug is dispensed to patients only in certain health care settings (e.g., infusion settings, hospitals);</li> <li>• Documented evidence of safe-use conditions before dispensing (e.g., lab test results)</li> <li>• Patients using the drug are subject to certain monitoring</li> <li>• Patients using the drug are enrolled in a registry</li> </ul>
<b>Implementation Plan</b>	A system to monitor and evaluate those who are responsible for implementing certain ETASUs.	<ul style="list-style-type: none"> <li>• Certification of distributors who distribute the drug to certified pharmacies or other certified settings</li> </ul>

Implementation of a REMS program can take many forms. Depending on the elements of the program, sponsors may need to provide health care professionals with approved REMS training materials (either in hard copy or online content) or support services, such as a call center to facilitate implementation.

Sponsors must also provide a plan for ongoing assessment of the REMS program once it is in place, which is included with the original REMS program proposal. At a minimum, assessments must be conducted 18 months, 3 years, and 7 years after the REMS program has been approved, though more frequent assessments are usually required for REMS with ETASU. The methodology used as part of the REMS Assessment Plan is also typically reviewed by FDA, either as part of the original REMS program proposal or prior to the first assessment.

Every REMS program has a stated goal and objectives against which it can be evaluated.<sup>7</sup> The REMS may be modified to add or eliminate an element if the REMS assessment shows that the program is not functioning as intended, if new safety information becomes available, or to reduce the burden to the health care delivery system. Drug sponsors may submit a request for modification at any time, and may also submit additional voluntary assessments of the REMS outside of the required assessment timetable.<sup>8</sup>

### **Provider Education as a Component of REMS**

Communication to providers or prescriber education for drugs with a REMS can take several forms, and may be required in some programs. As part of a Communication Plan, provider education can include REMS letters directed at health care providers, online resources, and other publications aimed at informing the relevant audience. For some drugs with a REMS that includes an ETASU, providers may be required to obtain certain training or certifications in order to prescribe or dispense the drug. This training may be delivered online or in-person, and often includes a knowledge assessment component designed to ensure the provider understands the material. Providers may also have to complete a separate enrollment form in order to be certified and able to prescribe the drug.

For example, the REMS program for Kynamro (a drug used in the treatment of a rare lipid disorder), includes a mandatory prescriber education requirement.<sup>9</sup> This training contains several components, all of which are available through the Kynamro REMS website, including: 1) a slide deck with an overview of the drug and the risks associated with it, as well as a self-administered knowledge evaluation; 2) a separate checklist prescribers can use to support patient monitoring; and 3) detailed prescribing information (e.g., dosing and administration, contraindications, information on use in specific populations, etc.).<sup>10</sup> The goal of this training is to ensure that the prescription of Kynamro is limited to prescribers who have been made aware of Kynamro's risks and the relevant strategies for mitigating those risks. After reviewing this information, prescribers must attest to having completed the training through the Kynamro REMS website (administered by Genzyme, the drug's manufacturer), after which they are permitted to prescribe the drug. No continuing education credits are awarded for successful completion of this training program.

A second example is the REMS program developed for extended-release/long-acting (ER/LA) opioid analgesics (a class of analgesic drugs commonly used to manage moderate to severe chronic pain). It includes a prescriber education component, though prescribers are not required to complete the training in order to prescribe these drugs. This program is described in greater detail below.

### *Development and Implementation of REMS CE for ER/LA Opioids*

The ER/LA opioid REMS program is part of a larger initiative within FDA's Center for Drug Evaluation and Research (CDER) to manage the safety concerns associated with opioid prescription and use. While these drugs can be effective for pain management, they also have serious risks, including addiction, accidental overdose, and death. Between 1999 and 2011, the death rate from opioid overdose quadrupled, and of the 43,982 total drug overdose deaths in the United States in 2013, 16,235 (37%) were due to opioid analgesics.<sup>11,12</sup> As part of a broader effort to address the widespread and growing problem of prescription opioid abuse and misuse, FDA required a class-wide REMS be established to provide information and education to both prescribers and patients on ER/LA opioids.<sup>13</sup>

First approved in July of 2012, the ER/LA opioids REMS program includes the following elements:

- 1) Prescriber training on ER/LA opioids
- 2) A Patient Counseling Document
- 3) A Medication Guide for each ER/LA opioids product<sup>14</sup>

Unlike most REMS prescriber education programs, which are provided directly by sponsors, this was the first REMS program to have prescriber training offered via accredited CE providers. FDA assumed the responsibility of creating a comprehensive listing of information that needed to be communicated to prescribers via the CE modules. This framework module, referred to as *the FDA Blueprint for Prescriber Education for ER/LA Opioids*, was drafted by FDA and posted for public comment before being finalized. The *Blueprint* includes information on assessing patients for possible ER/LA opioid treatment, initiating, managing, and discontinuing a patient's ER/LA opioid use, ways to counsel patients on the risks of ER/LA opioids, and detailed information about specific ER/LA opioid drugs.<sup>15</sup> The final *Blueprint* was made publicly available for any CE provider to use to create "REMS-compliant" CE modules. Modules are considered "REMS-compliant" if they fulfill the following requirements:

- 1) The CE training is offered by an accredited provider of continuing education,
- 2) The training covers all elements of the FDA *Blueprint*
- 3) The CE activities include a knowledge assessment of all sections of the FDA *Blueprint* after the activity is completed, and
- 4) The training is subject to independent audit to ensure all of the REMS training conditions are being met<sup>16</sup>

REMS-compliant CE activities are developed by accredited CE providers, and funding is available via grants for these activities from the REMS Program Companies (RPC), a consortium of ER/LA opioid manufacturers who collaborated to fund and implement the ER/LA Opioid REMS program that can be shared and used for any ER/LA opioid product.<sup>17</sup> Currently, there are 15 brand name and 31 generic drug products covered by this REMS program.<sup>18</sup> The first CE modules for this REMS program became available in March 2013, and as of September 2014 there were 62 CE providers offering 211 REMS-compliant CE activities.<sup>19</sup>

### *Evaluation and Monitoring of ER/LA Opioid REMS CE*

The RPC is responsible for assessing the performance of the REMS and reporting the results of the assessments to FDA, including the number of prescribers who have taken the training. CE providers are required to administer assessments at 6 and 12 months post-training in order to measure knowledge retention and prescriber practice changes. Using the data from these assessments, FDA intends to

identify where the gaps in understanding persist and in which prescribers those gaps are most prevalent.<sup>20</sup>

FDA has also set performance targets for this prescriber training. Within the first two years of implementation (slated to begin no later than March 1, 2013), the goal is to train 80,000 (25%) of the roughly 320,000 providers who, as of 2011, actively prescribe ER/LA opioid analgesics each year. This number climbs to 160,000 (50%) of ER/LA opioid prescribers by year three, and to 192,000 (60%) by year four.<sup>21</sup> The RPC will be submitting information on the first training performance goal as part of its July 2015 REMS assessment report.

### **REMS Continuing Education Initiative**

Previous assessments have shown that REMS training programs and communication plans are not having the desired effect on prescribers' knowledge of the risks associated with REMS drugs, and have further found that participation rates are low for training programs that are not linked to REMS requirements for prescribing or distribution.<sup>22</sup> Stakeholders have also raised concerns over the burden of REMS elements, arguing that prescribers may choose not to prescribe the drug rather than conform to requirements such as mandatory prescriber training.

In response to these issues, the REMS Integration Initiative was created in 2011 to improve and better evaluate the development, implementation, and assessment of REMS programs. When the Food and Drug Administration Safety and Innovation Act of 2012 re-authorized PDUFA V, the REMS Integration Initiative was folded into the agency's commitments. As part of this, FDA pledged to continue its work to evaluate and standardize REMS processes, and to work with stakeholders to integrate REMS into the current health care system.

In pursuit of this broader goal, the agency also agreed to undertake projects within each of four priority areas, one of which focused on improving provider education related to drugs with a REMS attached. During FDA's stakeholder engagement efforts, several groups expressed support for delivering REMS education through accredited CE providers, and asked FDA to facilitate this effort as part of its strategy to address some of the deficiencies in the current program.<sup>23,24</sup>

#### *Accredited CE as a Potential REMS Tool: Opportunities and Challenges*

Though specific requirements vary widely, nearly all states require health care professionals to undergo continuing education in order to maintain their licensure. This education can take a number of forms—including online programs, in-person events, and written publications—and is developed and delivered by several thousand independent accredited providers across the country. These providers include a broad range of organizations, such as hospitals, universities, medical societies, non-profit groups, insurance companies, and many others.<sup>25</sup> Tapping into this extensive national network could help to increase both the reach and the effectiveness of REMS provider education. Furthermore, the ability to earn educational credits might further incentivize providers to undertake the training.

Although FDA has prior experience with developing and implementing the class-wide REMS CE module for ER/LA opioid analgesics, this proved to be a burdensome and time-intensive effort, and one that the agency is likely unable to repeat for each drug that might have a REMS provider education requirement.<sup>26</sup> Furthermore, most REMS apply to a single drug rather than an entire class of drugs, and stakeholders have raised several questions over how to integrate CE into the REMS toolkit in such a case.<sup>27</sup>

For example, it is unclear what process should be established for developing CE content, and what the respective roles of FDA, industry, CE providers, and CE accrediting bodies should be within that process. Industry stakeholders have indicated that—given both their comprehensive knowledge of the risks posed by their own drug as well as their statutory responsibility to execute REMS program commitments—they should have input on the content of future REMS CE modules.<sup>28</sup> However, industry involvement in content might be challenging to reconcile with the standards of commercial independence and conflict of interest established by the three main CE accrediting bodies.<sup>29</sup> There are also questions related to the content itself, what it should include, and how much flexibility providers should have in tailoring the content to suit the audience. For example, the educational needs of a specialist (such as an oncologist or anesthesiologist) are different from those of a primary care physician when it comes to opioid analgesic prescribing and management. Some have further suggested that single-drug REMS content be embedded within a larger framework (such as education on adverse event recognition and reporting components, or benefit-risk assessment and communication more generally) rather than simply on the risks of the drug.<sup>30</sup> Others have noted that future REMS CE should, to the extent possible, reflect the team-based nature of care rather than focusing solely on prescribers, as was the case with the ER/LA opioid analgesic REMS.<sup>31</sup>

Other key questions relate to implementation and provider uptake. Providers have limited time and many hundreds of options when it comes to obtaining CE credit, and it may be necessary to identify supportive strategies that could help to promote REMS content and ensure that it meets the needs of the intended audience. The process for establishing provider uptake targets will need to be clarified and refined in order to ensure that these targets are feasible. More work is also required to determine the broader outcomes that should be used to monitor and evaluate the impact of the REMS, and what systems are necessary to support the collection and reporting of that data.

### **Workshop Objectives and Discussion Questions**

In light of these ongoing questions, the Center for Health Policy at the Brookings Institution through a collaborative agreement with FDA is convening a workshop in order to explore the feasibility of incorporating CE activities into single-drug REMS. This workshop will provide an opportunity for pharmaceutical manufacturers, regulators, CE providers, accreditors, and other stakeholders to explore the ways that CE can be a valuable addition to the REMS toolkit, discuss potential barriers to the development and implementation of REMS-related CE for single products, and identify strategies for addressing those barriers. This discussion will include the use of two case studies, which will help to frame the issues in both the pre- and post-market setting. (See Appendix). Further information on the structure of the day and the questions that will be addressed is provided below.

### **Lessons from the ER/LA Opioid Analgesic REMS Development Process**

This forty-five minute session will consist of three brief presentations that will introduce and discuss the major lessons learned from the ER/LA Opioid Analgesic REMS CE project; with a particular focus on those lessons which are directly applicable to single drug REMS.

### **Session I: Defining the Added Value of CE as Part of the REMS Toolkit**

This session will identify the essential elements that would need to be in place to ensure that CE is a meaningful and valuable addition to the REMS toolkit. This session will help to frame the ensuing discussion, which will focus on specific strategies that would ensure those elements are put into place. Specific issues to address could include:

- Ensuring content development meets the needs of FDA, sponsors, and the intended audience for the training
- Determining the desired outcomes of provider training through CE (i.e. provider uptake, behavior change, etc.)
- Ensuring accountability for meeting those outcomes at the sponsor, accreditor, and provider level
- Reporting systems that could help to support monitoring and evaluation
- Ensuring the REMS CE development and implementation processes take into account the team-based nature of health care, and allow others to leverage REMS CE to their greatest advantage.

### **Session II: CE Programs for Single Drug REMS: Developing Valid and High-Impact Content**

Using two case studies, this session will identify the major barriers related to CE content development, and explore specific strategies that could help to address those barriers in both the pre- and post-market setting. Questions to address would include:

- The respective roles of the FDA, industry, CE providers, and CE accrediting bodies in determining the format, delivery method, length, etc., of a CE program
- Addressing potential conflicts of interest in REMS CE content development
- Viable options for a drug company to fund a CE program(s) through a CE provider that specifically aligns with the REMS materials and labeling
- Identifying accreditation criteria that could create obstacles, as well as possible solutions to those barriers
- Building quality control into the content development process to ensure CE materials adequately address the risks identified in the REMS
- Establishing a process for updating REMS CE content requirements based on new evidence
- Incorporating product-specific REMS CE into larger education programs (such as those aimed at a particular cohort of prescribers)
- Consider methods of tailoring REMS CE content to address the needs of various audiences, and/or consider feasibility of a “testing-out” option
- Considerations for addressing when CE could be done through a single program (i.e. sponsor contracts directly with a CE provider to develop one program) versus multiple programs (i.e. programs developed through a request for proposal (RFP); e.g. the ER/LA opioid REMS)

### **Session III: CE Programs for Single Drug REMS: Best-Practices for Implementation and Uptake**

Using the same two case studies, this session will identify the major barriers related to implementation and provider uptake, and identify specific strategies to address those barriers in both the pre- and post-market setting. Specific questions to address could include:

- Approaches to developing feasible targets for prescriber uptake
- Establishing processes for accountability to ensure uptake targets are met
- Viable funding streams to support CE activities
- Articulating clear consequences and potential contingency strategies in the event that uptake falls short of stated goals
- Identify supportive strategies to incentivize prescriber uptake (improved communication strategies, better alignment with state licensing boards, other government agency requirements, payment incentive strategies.)

- Consider the IT infrastructure necessary to collect data regarding uptake and other outcomes of interest
- Determine the data elements that should be collected, and potential approaches to defining that data

#### **Session IV: Identifying Other Key Facilitators and Barriers to REMS CE Development and Uptake**

This session will be used to identify and explore additional issues, barriers or strategies that have not previously been raised, but which have implications for the successful development and implementation of REMS CE.

#### **Session V: Major Takeaways and Next Steps**

This final session will be used to identify outstanding questions that were raised throughout the day and require further discussion. Discuss potential next steps that FDA and other stakeholders can take with regard to implementing the REMS CE initiative. Questions to address could include:

- Criteria that can be applied to determine whether a REMS CE is the most appropriate approach to mitigating drug risks?
- Monitoring the progress and uptake of single-drug REMS, as well as approaches to evaluating their effectiveness.



## Appendix I: Hypothetical REMS Case Studies to Guide Discussion

### Objective

Identify strategies to address the challenges/barriers to developing a continuing education (CE) program for two fictitious drugs: Allnatine, which would be developed in a pre-approval setting, and Vomarumab, which would be developed in a post-approval setting. Though these case studies are fictitious, they include serious risks that could be addressed by a REMS.

### Key Considerations for Discussion

- The respective roles of the FDA, industry, CE providers, and CE accrediting bodies in determining the format, delivery method, length, etc., of a CE program.
- Addressing potential conflicts of interest in REMS CE content development.
- Viable options for a drug company to fund a CME program(s) through a CME provider that specifically aligns with the REMS materials and labeling.
- Identifying accreditation criteria that could create obstacles, as well as possible solutions to those barriers.
- Potential methods/approaches to conveying the essential information related to the risks.
- Building quality control into the content development process to ensure CE materials adequately address the risks identified in the REMS.
- Establishing a process for updating REMS CE content requirements based on new evidence.
- Incorporating product-specific REMS CE into larger education programs (such as those aimed at a particular cohort of providers).
- Consider methods of tailoring REMS CE content to address the needs of various audiences, and/or consider feasibility of a “testing-out” option.
- Communicating the essential information while minimizing burden to the health care provider (e.g., both in terms of time and ease in accessing the training).
- Potential strategies for developing a CE program within the framework of the drug approval process. In a pre-approval setting, this includes consideration of both the timeframe to develop a REMS CE program (approximately four months) as well as the associated confidentiality issues.
- Discuss the approaches, as well as the potential advantages and disadvantages, of developing a single CE program (i.e., sponsor contracts directly with a CE provider to develop one program) versus multiple CE programs (i.e., programs developed through a request for proposal; e.g. the ER/LA opioid analgesics REMS).
- Ensure the REMS CE development process take into account the team-based nature of health care.

### Case Study #1 – Pre-Approval REMS: Allnatine

Allnatine is proposed for the treatment of adult patients with acute lymphoblastic leukemia (ALL). It is an intravenous solution administered continuously for 7 days. If approved, this would be the first in class for the treatment of ALL. Allnatine is associated with a risk of progressive respiratory paralysis which has resulted in fatal events. It is important to interrupt therapy at the first sign of shortness of breath. If treatment is stopped early the paralysis may be reversible.

Training and education will be required for health care providers who are responsible for prescribing, dispensing, or administering Allnatine.

#### **Risk information to be conveyed to health care providers:**

Mitigate the risk of progressive respiratory paralysis associated with Allnatine by educating health care providers of the following:

- appropriate patient selection
- the serious risk of progressive respiratory paralysis and the need to immediately interrupt or stop therapy at first signs of shortness of breath

The likely prescribing population will be oncologists. It will be used primarily in an inpatient setting.

Potential challenge to consider: completing all or some of the components of the CE development activities prior to approval due to the short timeframe and confidentiality-related issues.

### Case Study #2—Post-approval REMS: Vomarumab

Vomarumab is an inhalation powder approved in 2013 for the treatment of acute exacerbations of severe and debilitating vertigo. After marketing, FDA learned of new safety information related to Vomarumab and the risk of acute bronchospasm in patients with chronic lung disease which can be severe and life-threatening. Vomarumab will be required to have a REMS to ensure the benefit outweighs the risk of acute bronchospasm.

Training and education will be required as part of the REMS; providers will not be able to prescribe the drug until they document their training.

#### **Risk information to be conveyed to health care providers:**

Mitigate the risk of acute bronchospasm associated with Vomarumab by educating health care providers of the following:

- acute bronchospasm has been observed with Vomarumab in patients with asthma, chronic obstructive pulmonary disease (COPD) and patients with a history of smoking

- the drug is contraindicated in patients with chronic lung disease
- patients should be evaluated for lung disease before starting on Vomarumab

The likely prescribing populations could include neurologists, ear nose and throat specialists, family practitioners, and internists. It may be used in both acute care and ambulatory settings with or without direct healthcare provider supervision.

Potential challenges to consider: the need to have different training programs due to the potential for variability in provider knowledge related to the management of the acute risk given the drug's use in acute and ambulatory settings; and the potentially large and diverse provider population.

<sup>1</sup> Reinke, Thomas. (2011). "Stakeholders Say FDA Must Change REMS Program." *Managed Care Magazine*. Retrieved May 9<sup>th</sup>, 2015, from <http://www.managedcaremag.com/archives/1103/1103.medmgmt.html>.

<sup>2</sup> U.S. Food and Drug Administration. (2014). *Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS)*. Retrieved May 9<sup>th</sup>, 2015, from <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM415751.pdf>.

<sup>3</sup> [Ibid.](#)

<sup>4</sup> U.S. Department of Health and Human Services. (2005). *Guidance for Industry: Development and Use of Risk Minimization Action Plans*. Retrieved May 9<sup>th</sup>, 2015, from <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126830.pdf>.

<sup>5</sup> U.S. Department of Health and Human Services. (2009). *Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*. Retrieved May 9<sup>th</sup>, 2015, from <http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf>.

<sup>6</sup> U.S. Food and Drug Administration. "Approved Risk Evaluation and Mitigation Strategies (REMS)." Retrieved May 9<sup>th</sup>, 2015, from <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>.

<sup>7</sup> Choe, Lena Y. "Risk Evaluation and Mitigation Strategies." U.S. Food and Drug Administration. Retrieved May 9<sup>th</sup>, 2015, from <http://www.fda.gov/downloads/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/PharmacyStudentExperientialProgramCDER/UCM276838.pdf>.

<sup>8</sup> U.S. Department of Health and Human Services. (2009). *Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*. Retrieved May 9<sup>th</sup>, 2015, from <http://www.fda.gov/downloads/Drugs/Guidances/UCM184128.pdf>.

<sup>9</sup> U.S. Food and Drug Administration. (2013) Kynamro REMS Approval Letter. Retrieved May 9<sup>th</sup>, 2015, from <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM337472.pdf>.

<sup>10</sup> Kynamro Risk Evaluation and Mitigation Strategy. Retrieved May 9<sup>th</sup>, 2015, from <http://www.kynamrorems.com/>.

<sup>11</sup> Chen, Lui Hui, et. al. (2014). "Drug-poisoning Deaths Involving Opioid Analgesics:

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United States, 1999–2011.” Centers for Disease Control and Prevention. Retrieved May 9<sup>th</sup>, 2015, from <http://www.cdc.gov/nchs/data/databriefs/db166.htm>.

<sup>12</sup> Centers for Disease Control and Prevention. “Injury Prevention & Control: Prescription Drug Overdose.” Retrieved May 9<sup>th</sup>, 2015, from <http://www.cdc.gov/homeandrecreationalafety/overdose/facts.html>.

<sup>13</sup> U.S. Food and Drug Administration. “Questions and Answers: FDA Requires a Risk Evaluation and Mitigation Strategy (REMS) for Long-Acting and Extended-Release Opioids.” Retrieved May 9<sup>th</sup>, 2015, from <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm251752.htm>.

<sup>14</sup> U.S. Food and Drug Administration. (2012). “Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS).” Retrieved May 9<sup>th</sup>, 2015, from <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf>.

<sup>15</sup> U.S. Food and Drug Administration. (2014). “FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics.” Retrieved May 9<sup>th</sup>, 2015, from <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf>.

<sup>16</sup> Accreditation Council for Continuing Medical Education. (2015). “Accredited Continuing Medical Education and the Food and Drug Administration’s Risk Evaluation and Mitigation Strategies.” Retrieved May 9<sup>th</sup>, 2015, from [http://www.accme.org/sites/default/files/660\\_20150106\\_REMS\\_Fact\\_Sheet.pdf](http://www.accme.org/sites/default/files/660_20150106_REMS_Fact_Sheet.pdf)

<sup>17</sup> ER/LA Opioid Analgesics REMS Frequently Asked Questions. Retrieved May 9<sup>th</sup>, 2015, from <http://www.er-la-opioidrems.com/lwgUI/rems/faq.action>.

<sup>18</sup> “Products covered under the ER/LA Opioid Analgesics REMS Program.” Retrieved May 9<sup>th</sup>, 2015, from <http://www.er-la-opioidrems.com/lwgUI/rems/products.action>.

<sup>19</sup> Accreditation Council for Continuing Medical Education. (2014). ER/LA Opioid REMS CME Activities in PARS.” Retrieved May 9<sup>th</sup>, 2015, from [http://www.accme.org/sites/default/files/645\\_20140916\\_PARS\\_REMS\\_Data\\_Rpt\\_0.pdf](http://www.accme.org/sites/default/files/645_20140916_PARS_REMS_Data_Rpt_0.pdf).

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<sup>27</sup> Public docket response to the Standardizing REMS Report, see: <http://www.regulations.gov/#!docketBrowser;rpp=100;so=DESC;sb=docId;po=0;dct=PS;D=FDA-2013-N-0502>

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