

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

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Meeting Summary

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 developed into an important tool to ensure that the benefits of a particular drug outweigh its associated risks and has permitted FDA to approve products that otherwise might not have been available for patient use.¹ As part of its commitments under the Prescription Drug User Fee Act of 2012, FDA is currently undertaking multiple efforts to improve and standardize the REMS program, including investigating the possibility of delivering provider training via accredited continuing education (CE) for single-drug REMS.

Risk Evaluation and Mitigation Strategies

FDA can require that a REMS be developed for a drug before it is approved, or it can be required post-approval if new safety information indicates there is a severe risk of adverse events associated with it. The drug's manufacturer is responsible for designing, implementing, and evaluating their REMS program. As of September 22, 2015, there are 76 active REMS programs for individual drug and biologic products in place and seven shared system REMS that apply to an single drug or class of products.²

A particular REMS can include one or more elements as well as a diverse set of materials and processes (collectively called 'tools') to help mitigate a drug's risks:

- 1) Medication Guide or Patient Package Insert (PPI)
 - FDA-approved patient labeling.
- 2) Communication Plan
 - Communications (e.g., Dear Health Care Provider letters) to health care providers such as physicians, pharmacists, nurses, and physician assistants.
- 3) Elements to Assure Safe Use (ETASU)
 - Prescribers may need specific training/experience or special certifications;
 - Pharmacies, practitioners, or health care settings that dispense the drug may be specially certified;
 - The drug may be dispensed only in certain health care settings (e.g., infusion settings, hospitals);
 - The drug is dispensed to patients with evidence of safe-use conditions such as laboratory test results;
 - Each patient using the drug may be subject to monitoring

- Each patient is enrolled in a registry.
- 4) Implementation system
- System to monitor and evaluate implementation of ETASU.

Depending upon the particular elements, sponsors are required to equip health care providers with various resources to help implement the REMS. These can include training materials or support services such as call centers to answer questions and facilitate implementation. Sponsors must also provide a plan for ongoing assessment of the REMS once it has been put in place, and assessments must be conducted at a minimum of 18 months, 3 years, and 7 years after the REMS is approved. REMS include stated goal(s) against which they can be evaluated, and sponsors may submit additional voluntary assessments at any time. If the REMS assessments show that the program is not functioning as intended, if new safety information becomes available, or if the burden to the health care delivery system needs to be reduced, the REMS may be modified in response.

Provider Education as a Component of REMS

Provider education as part of a REMS can take a number of forms. Communication plans, for example, may include letters with REMS information aimed at health care providers, publications in professional medical journals, or online educational resources. For REMS with an ETASU, providers may be required to undergo REMS-specific training or become specially certified. For some REMS, prescriber training may be linked to dispensing of the drug. Training is typically offered either online and/or in-person, and participants may need to complete an assessment after finishing the training to show that they understood safety and risk messages.

In certain REMS programs, prescriber training may be mandatory. For example, the drug Kynamro (used in the treatment of a rare lipid disorder) has a REMS that requires prescribers to undergo training on the drug's risks as well as the appropriate strategies for mitigating those risks. After taking the training (found on Kynamro's REMS website) prescribers must complete an enrollment form that attests that they have completed the training before becoming certified in the REMS program. This ensures that Kynamro is prescribed only by those prescribers who have been made aware of its risks and the appropriate methods for mitigating those risks.

In other cases, prescriber training is available but may not be required. For example, the extended-release/long-acting (ER/LA) opioid analgesics REMS program—a class of drugs commonly used to treat moderate to severe chronic pain—makes prescriber training available but does not require providers to complete the training in order to prescribe from this class of drugs. The ER/LA opioid analgesics REMS program is also the first to offer a training program that includes accredited continuing education (CE). As part of the development process for this REMS, FDA created a framework, known as *the FDA Blueprint for Prescriber Education for ER/LA Opioids*, that included all of the relevant information that the CE module should contain. This Blueprint was made publically available for CE providers to use in designing “REMS-compliant” CE modules (that is, the training is provided by an accredited provider, it covers all elements of the Blueprint, includes a knowledge assessment component, and is subject to independent

audit). Prescribers who complete these modules could then earn CE credit towards their state medical licensure requirements. Currently, there are 14 brand name and 40 generic drug products covered by this REMS program.³ The first CE modules for this REMS program became available in March 2013, and as of July 2015 there were 82 CE providers offering 449 REMS-compliant CE activities.⁴

REMS Continuing Education Initiative

In response to stakeholder concerns over the effectiveness and associated burden of REMS—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 program and to better integrate REMS tools into the health care system.⁵ In September 2014, after extensive consultation with stakeholders, FDA announced four priority projects it will pursue as part of its REMS reform efforts, one of which focuses on health care provider education under REMS.⁶ Past assessments have indicated that REMS training programs and communication plans are not having the desired impact on prescribers' knowledge of the risks associated with REMS drugs and have also shown that participation rates are low for training programs that are not linked to REMS requirements for prescribing or distribution.⁷ A number of stakeholders have shown support for broader use of accredited CE providers to deliver REMS education (beyond the existing class-wide education program for ER/LA opioids), and FDA has committed to exploring whether this might be a viable method of addressing some of the issues surrounding current REMS educational elements.^{8,9}

Meeting Objectives

In support of this priority project, and under a cooperative agreement with FDA, Brookings hosted an expert workshop on May 18, 2015, which explored the feasibility of integrating accredited continuing education into REMS programs for a single drug. This workshop included representatives from brand and generic companies, CE providers, health care provider organizations, and CE accrediting bodies. An agenda and a list of participating panelists are available [here](#). A summary of the workshop discussion is outlined below.

Essential Elements of CE: Defining the Added Value of CE as Part of the REMS Toolkit

The day's discussion began with a consideration of the essential elements that would need to be in place for CE to add value to the REMS. A number of participants emphasized that careful planning and forethought at each step of the CE process will be crucial to ensuring that CE will be a successful REMS component. It will be important to determine whether CE would be the optimal approach to meeting the goals of a REMS. If CE was found to be the right tool, the gaps in knowledge and practice will need to be clearly identified and any potential barriers to closing those gaps assessed so that the CE content will sufficiently address the issues at hand. Additionally, the metrics used to evaluate the CE should also be laid out early in the development process, and should reflect useful outcomes such as provider competence, changes in practice, or even changes in patient outcomes.

A recurring theme was the importance of early dialogue between stakeholders, which was seen as being crucial in order to build trust, accountability, and address any barriers. Several

participants noted that more communication between FDA and CE providers in particular would be beneficial, as it might help to address some of the concerns raised regarding the FDA's ER/LA Opioid Blueprint. This module was seen by many participants as being too rigid and didactic and too narrowly focused on prescribers. Participants further suggested that the audience for any future REMS CE would need to be broadened in order to reflect the increasingly team-based nature of health care. However, FDA mentioned the statute as being a limiting factor for requiring all members of the health care team to complete training versus the prescriber. Depending on the nature of the drug and its mode of delivery, a number of different health care professionals may potentially interact with a patient who is currently using a drug approved with a REMS. As such, the ability to tailor CE content to the needs and knowledge of those different health care professionals would be useful in increasing the effectiveness of CE content. Several participants also raised the possibility of integrating the risk information for a REMS drug within the context of information on other treatment options. Such an approach might help to incentivize uptake as well as address concerns that a CE program that focused on just one drug might be seen as promotional rather than educational. The cost-effectiveness of using CE to train providers would also need to be taken into account; participants stressed that offering the training for free (or at no more than a nominal fee) would be preferable, and noted that whether or not there is a cost to the provider may affect Sunshine Act reporting requirements.

In terms of monitoring and evaluating REMS CE, stakeholders noted the benefit of having flexible, real-time technology systems to collect data, as well as the ability to use that data to modify the CE program as necessary. Participants cited the Institute of Medicine's initiative to define and create a "Learning Health System" as an illustration of a pathway to leveraging health IT to increase the dissemination of information and improve health outcomes. Linking these technology systems to electronic medical records (EMR), for example, could help CE providers target their audience more efficiently. When a drug approved with a REMS is prescribed for a patient, an EMR notification could alert their health care provider that there is REMS CE training available for the drug. Participants also emphasized the importance of changing how REMS CE is evaluated. The success of the CE for the ER/LA opioid REMS was measured by the number of prescribers who completed the training. There was general agreement among participants that other key aspects such as competence and changes in practice need to be measured to truly gauge the impact REMS CE has.

Developing Valid and High-Impact CE Content

Participants discussed a range of challenges facing the REMS CE content development process and provided many potential approaches for working through them. Echoing sentiments from earlier sessions, many emphasized the importance of bringing CE providers into the content development process and having them assess the gaps in knowledge and practice that the CE needs to address. This will help ensure that REMS CE follows best practices in needs assessment and content development and prevents the content from becoming too didactic and focused purely on knowledge acquisition. However, some participants cautioned that, given the typical approval timeline for a new drug, it may be difficult to design REMS CE entirely during the pre-approval stage. Instead, CE could perhaps be a part of the elements of the REMS for a drug that

is decided upon pre-approval but with the understanding that the CE will become available in a certain amount of time after the drug and REMS are approved.

Issues surrounding conflicts of interest in content development were major subjects of discussion. Under current CE provider standards of independence, industry can have no say in the content of accredited CE regarding their product. Balancing those standards against the fact that industry knows the specific risks of their product better than other stakeholders will prove a complex situation to navigate. Participants offered several suggestions, such as having FDA create a standard outline of what risks need addressing for a given drug and allowing CE providers to design content around those risks. This would prevent FDA from shouldering the burden of creating an entire blueprint of required content as it did for the ER/LA opioid REMS. Alternatively, FDA could review and approve sponsor-generated content (similar to what it already does for labeling language), which then in turn could be used by CE providers.

Participants also suggested that there were ways for CE providers to incorporate REMS information on a single drug into other activities without needing an industry grant to create CE specifically and solely around that particular product. In that case, industry could instead support development of a standardized packet of information which could then be picked up and incorporated into a CE module. Some warned that it would be more difficult to measure the impact and outcomes of the education this way, but others pointed out that measurement fatigue in CE is already an issue, and it would be beneficial to avoid ‘recreational’ data collection where possible. Another option included bringing in some kind of independent, trusted agent to respond to Request For Proposals (RFPs) from CE providers so that industry does not get to decide which CE providers are to be awarded their grants. There was also general agreement that it would be feasible for the CE accrediting bodies to work to ensure standards for commercial support and independence apply to single drugs, with the accrediting bodies collecting data on single-drug CE activities and reporting out to both industry and FDA.

In terms of the content itself, participants stressed again the need to be able to tailor the information to various audiences and warned against requiring a “one-size-fits-all” approach to REMS CE. A “testing-out” option for health care providers who already have some knowledge on the topic area may be particularly useful in this regard. More providers may be willing to take and complete the CE if they can demonstrate their prior knowledge and skip some parts of the training that may otherwise be redundant. However, several stakeholders also reminded the group that effective continuing education cannot be one-and-done; REMS CE will need to take into account that the information on the risks of a drug need to be communicated to health care providers multiple times for them to be retained and to have the desired effect on knowledge and practice changes.

It was also suggested that it may be possible to adapt the information already contained in boxed warnings in order to create CE content and structure and to draw from past experience in implementing CE in the medical device field. In the late 1990s, FDA worked with CE accrediting bodies to develop post-purchase training on individual medical devices, which could be integrated into accredited CE. In that case, CE accrediting bodies were able to accommodate

the agency's need to focus on specific devices without compromising standards of independence and commercial support. Stakeholders generally agreed that it was certainly reasonable to infer that a similar process may be possible for a single drug REMS.

Best Practices for Implementation and Uptake

While there are a number of potential barriers to the implementation and uptake of REMS CE, participants identified several strategies for overcoming them. Sponsor representatives in particular cited lack of accountability as a main issue affecting the REMS CE process. Drug sponsors are directly accountable to FDA for achieving the goals of their REMS programs, but in the case of the ER/LA opioid REMS, industry had no means by which to ensure CE providers were hitting CE uptake targets. In the future it may be helpful to implement a milestone-driven accountability process for CE providers similar to other contract mechanisms employed in the industry.

Participants also cited room for improvement in the setting of CE uptake targets themselves. The targets set by FDA for the ER/LA opioid program were seen by some as being unfeasibly high, and it was suggested that a benchmarking process be established. Participants proposed having a central registry to collect participation data from all CE providers offering CE for a REMS, which would then enable more real-time tracking. A number of participants agreed that it would be valuable to simply expand upon the data standards already established by Medbiquitous for the ER/LA opioid REMS CE rather than create a new set of standards. By stratifying data by different types of health care provider, for example, CE providers could also see who is really taking the CE training and refine their uptake targets over time.

Many participants cautioned against making the CE mandatory in all cases, as that can lead to unintended consequences (e.g., providers might avoid prescribing the drug entirely rather than take the training). However, it was also noted that REMS CE programs must compete with hundreds of other modules, and FDA might consider specific strategies to help raise the profile of REMS. For example, a branding strategy that clearly identified the training as being FDA approved and REMS compliant might help REMS CE training stand out. Increasing the integration of REMS CE into existing educational requirements (such as those required for Maintenance of Certification or state licensure) would also increase the reach of REMS CE and further aid CE providers in achieving their uptake targets. Aligning REMS CE with these other requirements—perhaps by creating bridge courses that could help to fill gaps between the REMS and non-REMS content—would also help to reduce barriers to taking the training for health care providers and avoid making REMS CE an additional burden in terms of time or cost.

Stakeholders also stressed the importance of setting up sufficient performance metrics to focus more on elements like quality and performance improvement rather than simply the number of providers who complete the CE training. It was acknowledged that such a goal is challenging, as many of these outcomes only emerge over time and are not strictly dependent on CE. In general, CE providers determine what they need to measure with regards to their CE activities before they are even designed and work backward from that goal in order to ensure their activities have the desired impact on knowledge and practice.

Next Steps

Moving forward, stakeholders requested that FDA further define and clearly communicate the process by which the agency determines when accredited CE should be a part of a REMS. They also suggested that the agency offer additional guidance on what objectives CE is expected to accomplish as part of a REMS, particularly with regards to what competencies the CE is expected to target and what impact it is expected to have on its audience. Participants largely agreed that more clarification in these areas will help stakeholders understand what is expected of them and can help lead to more effective CE content.

Participants also reiterated the possibility of FDA consulting with state medical boards and medical specialty boards to explore whether there are opportunities to align REMS CE with pre-existing licensure or maintenance of certification requirements to offer providers additional incentives to take REMS CE activities. In addition, several participants emphasized the need to further consider the pros and cons of using CE alone versus using CE in conjunction with other safe-use initiatives in order to maximize the effectiveness of the interventions.

Overall, despite the many challenges raised throughout the day, participants were generally supportive of FDA's efforts to date and suggested that the agency continue to engage with the relevant stakeholders in order to further explore the suggestions raised during the day's discussion.

¹ Reinke, Thomas. (2011). "Stakeholders Say FDA Must Change REMS Program." *Managed Care Magazine*. Retrieved June 12th, 2015, from <http://www.managedcaremag.com/archives/1103/1103.medmgmt.html>.

² U.S. Food and Drug Administration. "Approved Risk Evaluation and Mitigation Strategies (REMS)." Retrieved September 22nd, 2015, from <http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>.

³ "Products covered under the ER/LA Opioid Analgesics REMS Program." Retrieved May 9th, 2015, from <http://www.er-la-opioidrems.com/lwgUI/remis/products.action>.

⁴ Accreditation Council for Continuing Medical Education. (2015). ER/LA Opioid REMS CME Activities in PARS: 2015." Retrieved September 28th, 2015, from http://www.accme.org/sites/default/files/708_20150825_PARS_REMS_Data_Rpt_Data.pdf

⁵ U.S. Food and Drug Administration. (2014). *Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS)*. Retrieved June 12th, 2015, from <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM415751.pdf>.

⁶ *Ibid.*

⁷ U.S. Food and Drug Administration. (2014). *Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS)*. Retrieved June 12th, 2015, from <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM415751.pdf>.

⁸ U.S. Food and Drug Administration. (2014). *Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS)*. Retrieved June 12th, 2015, from <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM415751.pdf>.

⁹ American Pharmacists Association. (2011). "Summary of the REMS stakeholder meeting on improving program design and implementation." *Journal of the American Pharmacists Association*, 51, 340-358. doi:10.1331/JAPhA.2011.11519 Retrieved June 12th, 2015, from <http://japha.org/article.aspx?articleid=1043939>.