

**REMS and Continuing
Education for
Health Care Providers**

FDA Feasibility Report

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REMS and Continuing Education for Health Care Providers – FDA Feasibility Report

EXECUTIVE SUMMARY

As part of the reauthorization of the Prescription Drug User Fee Act of 2012 (PDUFA V), the Food and Drug Administration (FDA) committed to efforts to standardize and assess the effectiveness of risk evaluation and mitigation strategies (REMS) and to better integrate REMS into the health care system. As part of those efforts, in September 2014, FDA issued the report *Standardizing and Evaluating Risk Evaluation and Mitigation Strategies* (REMS Standardization Report),¹ in which FDA identified four priority projects. One of those priority projects, which is the subject of this report, is to explore the feasibility of using accredited continuing education (CE) as the method for providing health care providers (HCPs) the training and/or education required under a REMS for individual new drug applications or biologics license applications (the CE Initiative).²

In preparing this report, the Agency obtained stakeholder feedback from multiple sources and activities, reviewed applicable published literature, considered the lessons learned from Agency experience with the REMS CE training program for extended-release and long-acting (ER/LA) opioid analgesics, and reviewed the results of a REMS CE-related exercise conducted by CE accrediting bodies.

FDA considered the feasibility of using accredited CE as the method for providing HCP education in two separate settings: (1) at the time of initial drug approval and (2) after drug approval when a decision is made to modify an existing REMS to include provider training and/or education that could be accomplished through a CE activity, or to require a REMS for the first time.

The Agency has concluded that CE can be a useful method for providing HCP education under a REMS. For drugs requiring a REMS, all components of the REMS must be operational before the drug can be marketed. Because of this requirement, it is generally not practical to incorporate CE as the method of providing HCP training at the initial time of approval, because doing so could delay the marketing of the product while the CE is developed. Information about draft labeling and the proposed REMS would not be available before approval because FDA does not disclose information about a drug that is under review, and pharmaceutical companies generally do not share with a third party (e.g., CE developer and/or provider) draft labeling or a proposed

¹ See FDA report *Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS)* September 2014, available at <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM415751.pdf>. Accessed September 2017.

² This report does *not* apply to new drug applications that would be required to join an established shared system REMS.

REMS that is not yet approved. Moreover, changes to the draft labeling and the proposed REMS can occur up to the time FDA approves the drug. Therefore, the time needed for an independent party to develop CE could cause a delay between approval and product launch.

However, integrating CE activities into REMS in a postapproval setting would not present the same potential for delay to product marketing and therefore appears to be more practical. CE activities could be included as part of a modification to an existing REMS or within a new REMS required postapproval if the Agency determines, based on new safety information, that a REMS is necessary.

FDA also believes that an FDA-developed *Blueprint* will need to be included in the REMS to guide CE providers on the risk messages, as well as on expectations as to when REMS requirements need to be implemented. In addition, stakeholders involved in CE development will need to consider and address the following issues when including CE as a component of the REMS.

- Minimizing HCP burden in complying with REMS requirements by ensuring that content of the training focuses on messages pertaining to the risks and safe use of the drug.
- Providing the CE activity in formats that are readily accessible to targeted HCPs.
- Ensuring that sufficient emphasis is placed on communicating the REMS risk information and REMS requirements and ensuring that this information remains current.
- Developing a process for documenting completion of the REMS CE and, when necessary, linking the completion of the CE to the appropriate REMS requirements.
- Assessing the effectiveness of the CE activity within the context of REMS assessments.

FDA welcomes the opportunity to work with pharmaceutical companies who wish to pursue incorporating CE into individual REMS programs.

I. BACKGROUND

A. Risk Evaluation and Mitigation Strategies (REMS)

The Food and Drug Administration Amendments Act of 2007 (FDAAA)³ added section 505-1 to the Federal Food, Drug, and Cosmetic Act (FD&C Act), which authorizes FDA to require a REMS for certain drugs if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.⁴ A REMS is a required risk management strategy that can include one or more elements to ensure that the benefits of a drug outweigh its risks.⁵

For example, a REMS can consist of a Medication Guide,⁶ a patient package insert,⁷ and/or a communication plan.⁸ FDA can also require certain elements to assure safe use (ETASU) as part of a REMS if it deems the elements to be necessary to assure the safe use of the product.⁹ The ETASU can include, for example, requirements that health care providers (HCPs) who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe-use conditions.¹⁰ The ETASU are not mutually exclusive and can be used in combination to support the goals of the program. Certain REMS with ETASU may also include an implementation system through which the sponsor is able to monitor and evaluate implementation of the ETASU and work to improve their implementation.¹¹ Finally, REMS must have a timetable for submission of assessments of the strategy for NDAs and BLAs.¹²

FDA can require a REMS before initial approval of a new drug application, or after the drug has been approved, if FDA becomes aware of new safety information¹³ and determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.¹⁴

B. HCP Education as a Component of REMS

Risk communication is a primary component of most REMS programs. It can occur through a communication plan developed by the pharmaceutical company to disseminate risk information to HCPs or as part of a training or educational program required as an ETASU. A REMS that contains ETASU can include training, education, or other mechanisms to support actions that HCPs who prescribe, dispense, and/or administer the drug must undertake to assure the safe use

³ Public Law 110-85.

⁴ See section 505-1(a) of the FD&C Act.

⁵ See section 505-1(e) of the FD&C Act.

⁶ Section 505-1(e)(2) of the FD&C Act.

⁷ Ibid.

⁸ Section 505-1(e)(3) of the FD&C Act.

⁹ See Section 505-1(f) of the FD&C Act.

¹⁰ Ibid.

¹¹ Section 505-1(f)(4) of the FD&C Act.

¹² See section 505-1(d) of the FD&C Act.

¹³ Section 505-1(b)(3) of the FD&C Act.

¹⁴ See section 505-1(a)(2)(A) of the FD&C Act.

of the drug. A REMS that contains a communication plan can employ a variety of methods to deliver messages to HCPs, including letters, information pieces, and REMS websites. A variety of methods have been used to train HCPs, including REMS program overviews, live presentations, online materials, and program brochures.

C. FDA's REMS CE Initiative

The REMS authority has enabled FDA to approve products with serious risks that might otherwise not have been made available to patients. However, since FDA's implementation of the REMS authority, concerns have arisen about potential impacts of REMS, particularly those with ETASU, on patient access to drugs and on the associated burden on HCPs and the health care system. Real or perceived burdens related to complying with REMS can discourage some HCPs from participating in such programs, thereby limiting patient access to the drugs.

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 undertook efforts to standardize and assess the effectiveness of REMS and to better integrate REMS into the health care system.¹⁵ As part of those efforts, in September 2014, FDA issued the report *Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS)* (REMS Standardization Report),¹⁶ in which FDA identified four priority projects it planned to pursue. One of the projects focused on incorporating accredited CE into individual REMS programs (i.e., REMS that are unique to a specific drug or biological product) that include a communication plan and/or HCP training components.

REMS communication plans and training programs that are part of ETASU are developed by the pharmaceutical company and are submitted to FDA for review. Once approved by FDA, the materials are made available to HCPs who are likely to prescribe or dispense the drug. In some cases, HCPs must complete training before they can either prescribe or dispense the drug. In other cases, REMS training is made available to HCPs, but participation in the educational activity is not a condition of being able to prescribe or dispense the drug.

Stakeholders have encouraged FDA to provide training in formats that are consistent with how HCPs stay up to date with medical or pharmaceutical information and have suggested that offering REMS training through CE activities could help encourage greater HCP participation. FDA was asked to explore the feasibility of this approach, and the Agency believes there is an opportunity to enhance current methods used in REMS to educate HCPs. REMS-based CE training could be effective in improving stakeholder participation in REMS programs both when training is voluntary for HCPs and when the training is required as a condition of prescribing and dispensing the drug.

¹⁵ PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017 (p. 26). Available at <http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm270412.pdf>. Accessed September 2017.

¹⁶ See FDA report *Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS)* September 2014. Available at <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM415751.pdf>. Accessed September 2017.

To date, the ER/LA Opioid Analgesics REMS is FDA's first and only experience using accredited CE in a REMS to fulfill the REMS requirement that training be made available to HCPs who prescribe ER/LA opioid analgesics. The pharmaceutical companies for these products provide unrestricted educational grants to accredited CE providers who offer CE courses to prescribers based on the content and messages of a *Blueprint* developed by FDA for this purpose. The lessons FDA has learned from the development and implementation of CE as part of the ER/LA Opioid Analgesics REMS are described in greater detail in section II.C.

The report that follows presents the results of FDA's assessment of the feasibility of incorporating CE as the method to provide HCP education in REMS programs.

II. PRIORITY PROJECT: REMS AND CONTINUING EDUCATION FOR HCPs

The goal of the CE Initiative was to determine the feasibility of using CE that meets the accreditation standards of the Accreditation Council for Continuing Medical Education (ACCME), American Nurses Credentialing Center (ANCC), and Accreditation Council for Pharmacy Education (ACPE) as a requirement in a REMS to provide HCP training or education.

This report describes FDA's collaboration with key stakeholders to help define a CE development process, identify potential barriers, and create a possible model for REMS-related CE. The Agency sought multiple opportunities to obtain stakeholder input, reviewed the published literature on the potential use of CE in REMS, and considered the lessons learned from its experience with the REMS CE training program for the ER/LA Opioid Analgesics REMS. FDA also considered results from a CE exercise conducted by the CE accrediting bodies.¹⁷ Each of these sources of information is discussed in the following sections.

A. Stakeholder Feedback on Incorporating Accredited CE into Individual REMS Programs

FDA solicited stakeholder feedback on the feasibility of integrating accredited CE into individual REMS programs. The Agency reviewed comments submitted in response to a *Federal Register* notice on the REMS Standardization Report,¹⁸ reviewed information discussed during an expert workshop sponsored by the Brookings Institution,¹⁹ and conducted follow-up discussions with stakeholders who attended the expert workshop and/or submitted comments to the *Federal Register* docket.

During the stakeholder engagement process, FDA heard similar and recurring themes. Comments highlighted important considerations and/or potential barriers to incorporating CE into individual REMS programs. The comments, as they relate to the REMS CE feasibility project, are summarized here.

¹⁷ The accrediting bodies discussed include the Accreditation Council of Continuing Medical Education, the American Nurses Credentialing Center, and the Accreditation Council for Pharmacy Education.

¹⁸ See www.regulations.gov, Docket No. FDA-2013-N-0502.

¹⁹ See meeting summary available at <https://www.brookings.edu/events/incorporating-continuing-education-into-single-drug-rems-exploring-the-challenges-and-opportunities/>. Accessed September 2017.

Feedback from CE Accrediting Bodies and Health Professional Organizations

The CE accrediting bodies and health professional organizations expressed support for the overall concept of incorporating CE into individual REMS programs. They also recognized the challenges posed by ACCME's Standards for Commercial Support,²⁰ which require that CE providers develop activities independent of commercial interests. The CE accrediting bodies suggested that CE program content be developed independently, based on the FDA-approved prescribing information, REMS goals and objectives, and risk messages contained in REMS materials. If a pharmaceutical company issues unrestricted educational grants to develop CE materials,²¹ this group of stakeholders believed that FDA should be responsible for stating the intended goals/outcomes of the CE activity. The CE accrediting bodies indicated that CE providers should determine the CE activity's content and format for the intended audience(s). For example, the content and format may be different depending on the HCP audience (e.g., specialist vs non-specialist) and should be delivered in such a way as to increase the likelihood of changing behavior and improving performance (i.e., point-of-care training).

Feedback from CE Providers

CE providers expressed support for developing REMS CE activities for approved drugs as well as for drugs pending FDA approval, with the REMS CE activity being published or presented at the time the drug is marketed.

CE providers also suggested that FDA consider adding a full listing of CE related to any given REMS-compliant courses on FDA's Website or offer some sort of recognition of *REMS compliance* for CE providers who develop REMS-compliant education.²² Such recognition could foster better communication on the value of being educated about REMS-related topics. The CE providers also advocated for resources to measure and evaluate the effect of the CE activity, such as by measuring changes in knowledge or impact on potential clinical decision-making or behavior before and after completion of the activity.

Feedback from Patient and Consumer Organizations

Patient and consumer organizations expressed concern about pharmaceutical companies' "desire to offer CE for individual drugs with REMS." Although pharmaceutical companies currently support the vast majority of CE programs through unrestricted educational grants, patient and

²⁰ ACCME's Standards for Commercial Support: Standards to Ensure Independence in CME Activities, available at <http://www.accme.org/requirements/accreditation-requirements-cme-providers/standards-for-commercial-support>. Accessed September 2017.

²¹ For the ER/LA Opioid Analgesics REMS, FDA requires manufacturers of ER/LA opioid analgesics, known as the REMS Program Companies (RPC), to make training available for prescribers of these medications. RPC-supported REMS training is provided through accredited CE activities supported by independent educational grants from these ER/LA opioid analgesic companies.

²² *REMS-compliant training* is a term used in the ER/LA Opioid Analgesics REMS. Training is considered REMS-compliant training if (1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers; (2) it includes all elements of the *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics* (FDA Blueprint); (3) it includes a knowledge assessment of all of the sections of the FDA Blueprint; and (4) it is subject to independent audit to confirm that conditions of the REMS training have been met.

consumer organizations often consider these educational efforts “more promotional than evidence based and clearly biased because of conflicts-of-interest.”²³

Feedback from the Pharmaceutical Industry (trade associations and individual pharmaceutical companies)

The pharmaceutical industry also expressed support for incorporating CE into individual REMS programs if the CE is part of a comprehensive REMS training program (i.e. not as the exclusive training delivery mechanism) and if pharmaceutical company involvement is permitted—as mentioned earlier, the ACCME’s Standards of Commercial Support preclude direct input from companies.

Industry commented that for a new molecular entity (NME), the drug sponsors may have the most experience with the product. The pharmaceutical industry believes that, without direct sponsor input, the CE provider would be challenged to be able to develop a program independently that sufficiently prioritizes and succinctly conveys critical risk information that is the focus of the REMS. Companies questioned how FDA would ensure that CE providers prominently incorporate the risk messages, REMS requirements, and/or operational aspects of a REMS (e.g., requirements for certification or enrollment into the CE program) and ensure that HCPs are getting the most up-to-date information. Companies expressed concern that because the ACCME’s Standards of Commercial Support do not permit the promotion of CE activities on pharmaceutical company Websites, it will be difficult for companies to create awareness of CE programs. An additional concern was how the REMS would be assessed if HCP uptake is low or the REMS goals were not being met.

Industry also advocated for better methods to assess the outcome of training as it relates to the REMS. When a company provides a grant to a CE provider, the company receives outcomes reports; however, the content of these reports may vary across CE providers and data can be difficult to aggregate and may also be subjective. Industry also noted that the cost of developing a CE activity could be a potential barrier for companies producing generic drugs; in particular, for a shared system REMS if the development cost is based on a company’s relative market share.

B. Literature on the Potential Use of Continuing Education

A review of the literature yielded several published systematic studies evaluating the role and impact of CE on prescriber knowledge, attitudes, and behavior and its effect on patient and population health outcomes. Published literature indicates that CE can improve prescriber knowledge, attitudes, and performance, as well as patient health outcomes.^{24,25} Educational strategies that are ongoing, interactive, and provide prompts or cues to action, such as protocols (e.g., physician order sets) or administrative or policy support (e.g. hospital policies or procedures), and those that are relevant to the learner were more likely to improve prescriber

²³ See www.regulations.gov, Docket No. FDA-2013-N-0502.

²⁴ Robertson MK, Umble KE, and Cervero RM. 2003. Impact of studies in continuing education for health professionals: update. *The J of Cont Ed in Health Professions* 2003;23: 146-156.

²⁵ Umble KE and Cervero RM. 1996. Impact studies in continuing education for health professionals: A critique of the research syntheses. *Eval Health Prof* 1996;19(2):148-174.

knowledge, attitudes, and performance and patient health status. A positive impact is more reliably seen on physician performance than on patient health outcomes, and greater improvement was demonstrated in physician performance and patient health when the CE was interactive or when multiple methods were employed.²⁶ For example, interactive techniques are more effective than didactic techniques while simulation methods are effective for improving psychomotor and procedural skills.³⁰

The Institute of Medicine (IOM) Committee on Measuring the Impact of Interprofessional Education on Collaborative Practice and Patient Outcomes examined the link between education and performance in practice, in particular the impact on patient and population health as well as health care delivery system outcomes.²⁷ They noted the difficulties in explicitly linking education to outcomes due to the lag time between interventions and outcomes and confounding factors that may interfere with implementation even if the HCP has the requisite knowledge. They recommended additional studies of the links between education, behavior, and outcomes.

Although results may vary, overall, the literature appears to support that CE can positively affect physician knowledge, attitudes, and performance as well as patient health status. If it is feasible to provide training or education through an accredited CE activity for certain individual REMS, CE accreditors will need to determine which CE activities will likely improve HCP performance and patient outcomes.

C. Lessons Learned from the REMS CE for ER/LA Opioid Analgesics

Throughout the REMS CE project, FDA, the pharmaceutical industry, and the CE community reflected on the collective experience in developing and implementing CE training for the ER/LA Opioid Analgesics REMS. This was the first time CE training was made available as part of a REMS.

As part of the development of the REMS, FDA established a basic outline and core messages document called the *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics*.²⁸ The FDA Blueprint is intended for use by CE providers when developing prescriber education on ER/LA opioid analgesics. The FDA Blueprint contains general information about selection and counseling of patients who may be using ER/LA opioid analgesics; specific information about the individual drugs in this class; and how to recognize the potential for and evidence of addiction, dependence, and tolerance. Key lessons learned are summarized below.

The Blueprint development process (from concept to final approval) took more than one year to complete. The draft Blueprint was announced through the issuance of a *Federal Register* notice on November 7, 2011, to obtain public comment. FDA then received and reviewed comments

²⁶ Cervero RC and Gaines J. 2014. Effectiveness of continuing medical education: Updated synthesis of systematic reviews. July 2014. Available at http://www.accme.org/sites/default/files/652_20141104_Effectiveness_of_Continuing_Medical_Education_Cervero_and_Gaines.pdf. Accessed September 2017.

²⁷ Institute of Medicine. 2015. Measuring the impact of interprofessional education on collaborative practice and patient outcomes. Washington, DC: *The National Academies Press* 2015.

²⁸ <http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm515636.pdf>. Accessed September 2017.

from over 60 individuals and organizations.²⁹ FDA also discussed the draft Blueprint at meetings of FDA's Drug Safety Oversight Board and consulted with the National Institute on Drug Abuse and the Substance Abuse and Mental Health Services Administration to ensure that the scope of the Blueprint was appropriate. Throughout the blueprint development process, FDA worked with ACCME and other accrediting bodies and CE providers to help ensure that accredited CE programs developed to comply with the REMS educational requirements would be in compliance with ACCME accreditation criteria and standards for commercial support.^{30,31}

The ER/LA Opioid Analgesics REMS (including the Blueprint) was approved July 9, 2012. The first REMS-compliant CE training was made available on February 28, 2013, approximately seven months after the approval of the REMS.

The Agency acknowledges that the time and process used to obtain public feedback on the draft Blueprint for the ER/LA Opioids Analgesic REMS may not be applicable to all products. However, FDA believes that the experience gained with the ER/LA Opioid Analgesic REMS regarding compliance with ACCME accreditation criteria and standards for commercial support can be directly applied to future REMS that include CE.

Other learnings from the process of developing the ER/LA Opioid Analgesic REMS CE include the following:

- Although a significant number of HCPs have been trained through this program, prescriber completion of the REMS-compliant training did not reach the targeted number of prescribers. The Agency recognizes there were many other educational activities that competed with the REMS-compliant CE programs for prescriber time.
- REMS CE providers, accrediting bodies, and learners expressed the need for more flexibility with regard to content to develop the types of education that is engaging to adult learners.
- The length of educational activities and the associated time commitment for completion, coupled with lack of a way to demonstrate prior knowledge or competency, may be discouraging prescribers from completing the REMS-compliant CE.

D. CE Exercise Conducted by CE Accrediting Bodies

To further assist FDA in determining the feasibility of developing a CE activity related to a REMS for an individual product, ACCME worked with ANCC and ACPE to conduct an exercise with volunteers from five accredited CE providers.

The CE providers that volunteered to participate were referred to a specific product's labeling and the approved REMS (REMS document and appended materials) available on the

²⁹ See www.regulations.gov, Docket No. FDA-2011-D-0771.

³⁰ Accreditation Council for Continuing Medical Education. 2016. Accreditation Requirements. Criteria for CME Providers-Accreditation Criteria. Available at <http://www.accme.org/requirements/accreditation-requirements-cme-providers/accreditation-criteria>. Accessed September 2017.

³¹ Accreditation Council for Continuing Medical Education. 2016. Accreditation Requirements. Criteria for CME Providers-Standards for Commercial Support. Available at <http://www.accme.org/requirements/accreditation-requirements-cme-providers/standards-for-commercial-support>.

REMS@FDA Website.³² The CE providers were asked to consider the target audience and answer a series of questions related to the approach they would take if they were going to be developing the CE activity for the product (e.g., purpose/objectives, program duration, format, hours required to develop the activity). However, the CE providers were not given specific instructions for the inclusion of any particular content, target audience(s), formats, or other specific information. The exercise was intended to give FDA a better understanding of the spectrum of possible program designs that could be developed by CE providers in the absence of FDA providing any specific guidance.

The results of the exercise generated a range of educational options based on the CE providers' approaches to educational design and their understanding of their usual audience(s). Of the five proposed CE activity descriptions, one focused solely on the risks associated with the use of the drug. Most of the programs proposed incorporating some information about the drug's risk(s) and information about the REMS within a broader educational review of the overall disease state, management of the disease, and the drug's use as part of that management. Other findings from the exercise included the following:

- The amount of time CE providers projected that would be required by the learner to complete the various CE activities ranged from 1 to 8 hours.
- The format of the proposed activities varied, including live courses, internet-based courses, and/or a live course migrated to an enduring internet-based format. Four of the five activities incorporated interactive case studies.
- The time and resource estimates of what would be required by CE providers to develop the CE activity varied widely, ranging from 65 to 1,000 hours.

Based on these findings, the Agency concluded that the time and resources needed to develop a CE activity will most likely vary, depending, for example, on the CE provider's existing activities and on whether content can be incorporated into a pre-planned activity (e.g., integrating the content into a specialty society's annual meeting or a hospital's regularly scheduled series) or has to be presented as a stand-alone. The format and time to complete may also depend on a CE provider's learners and their expertise with the subject matter.

The Agency also concluded that, in most circumstances, an FDA Blueprint will be needed to ensure that CE providers capture the risk messages and/or program requirements that are the focus of the REMS in the CE program.

III. CONTINUING EDUCATION IN REMS: KEY FEASIBILITY CONSIDERATIONS

FDA considered feedback from stakeholders, the summary of the literature, experience from the ER/LA Opioid Analgesics REMS, and the findings of the CE accreditors' exercise to evaluate the feasibility of using accredited CE as a method of providing HCP education under a REMS.

In general, stakeholders expressed support for the concept of incorporating CE into individual REMS, but had concerns about how this would be accomplished. FDA considered stakeholder

³² See <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>.

concerns with regard to developing CE that would include the risk and safety messages of the REMS, be independent of commercial interest, and be available at the time the drug is marketed without creating an undue delay in the availability of the drug.

FDA considered the feasibility of using accredited CE as the method of providing HCP education as a component of a REMS at two different time points in the drug approval and lifecycle process:

1. At the time of initial drug approval
2. After initial drug approval, either as a modification to an existing REMS, or in a new REMS required based on new safety information

FDA could require CE on its own initiative, or, alternatively, pharmaceutical companies could voluntarily submit proposals to include CE as a component of a REMS, either preapproval or postapproval.

The Agency's assumption was that the pharmaceutical companies would need to work through an unrestricted educational grant process to select the CE provider(s) to meet ACCME's Standards of Commercial Support, which require the CE provider to be independent of commercial bias when developing CE program content.

The following points were also considered and evaluated to determine, generally, if REMS-related CE would be feasible as the required method of providing HCP training under a REMS:

- Considering the timing of CE development within the timelines of REMS development, product approval, and the product lifecycle;
- Ensuring that accurate and up-to-date content (i.e., risk information, safe use conditions, information about the REMS) is available for inclusion and prioritized within the CE activity; and
- Defining the objectives of the CE activity and identifying metrics that would indicate success.

These points are addressed in more detail in the following sections.

A. CE as Part of a REMS at the Time of Initial Drug Approval

For drugs requiring a REMS at the time of initial drug approval, all components of the REMS must be operational before the drug can be marketed. The CE training would have to be designed, developed, and ready to go before the drug could be marketed and in most cases this development would not coincide with initial drug approval. This is because the information needed to develop the CE activities (labeling and risk information in the REMS) is not publicly available until drug approval. Information about draft labeling and the proposed REMS would generally not be available before approval because FDA does not generally disclose information about a drug that is under review, and pharmaceutical companies generally do not share with a third party (e.g., CE developer and/or provider) draft labeling or a proposed REMS that is not yet approved. Moreover, changes to the draft labeling and the proposed REMS can occur up to the time FDA approves the drug. Development of CE activities that are required as part of the REMS would have to take place after product approval but before marketing and could cause a delay between approval and product launch.

Last but not least, without FDA guidance, the CE program may not sufficiently emphasize REMS risk messages and requirements. To ensure the appropriate emphasis on communicating the REMS risk messages and requirements, FDA would have to provide guidance on information for the CE providers to include in the CE program (i.e., develop a FDA Blueprint for educational content), which would also take time.

B. CE as Part of a REMS Following Initial Drug Approval

In the postapproval setting, CE could be developed to provide training required as part of a modification to an existing REMS or as a component of a new REMS. For a drug that was initially approved without a REMS, CE could be developed as part of a new REMS required because FDA became aware of new safety information for that marketed drug.

For an existing REMS, if the Agency determines that a modification is necessary to ensure that the benefits of the drug continue to outweigh its risks, or to reduce the burden on the health care delivery system of complying with the REMS, the Agency could require incorporation of CE based on information from REMS assessments, postmarket use data, and/or stakeholder feedback about potential mechanisms to help facilitate HCP training.

The postapproval setting is more amenable than the preapproval setting to the use of CE to provide required HCP training under a REMS because the product is already on the market and the additional time necessary to develop CE will not affect patients' access to the drug. In such cases, the approved labeling, the approved REMS (REMS document and REMS materials), and the REMS assessment plan would all be publicly available and could be used to help guide the development of necessary REMS content for an educational program.

However, these materials alone may not be sufficient to ensure that REMS-related CE programs place the necessary emphasis on risk messages and activities that are the focus of the REMS. Therefore, FDA believes that an FDA-developed Blueprint will generally be needed to guide CE providers.

C. Additional Considerations for CE Providers

When considering the feasibility of incorporating, developing, and implementing CE into REMS, CE providers, pharmaceutical companies, and other stakeholders involved in the REMS CE development process face important challenges to ensuring that content about risk messages and REMS requirements are sufficiently conveyed while minimizing the burden on HCPs. Stakeholders need to consider and address the following issues when including CE as the required method of providing HCP education under a REMS.

- Sufficient emphasis needs to be placed on communicating risk information and REMS requirements and keeping this information up to date

Additional guidance beyond labeling and/or the REMS and the REMS assessment, such as an FDA Blueprint, will be needed to ensure that CE providers know with specificity the key risk messages, REMS requirements, and/or safe use conditions that are the subject of the REMS. In addition, pharmaceutical companies and CE providers must have mechanisms in place to ensure that the REMS-related content captured within an educational activity remains up to date. Throughout a drug's lifecycle, FDA may become aware of new safety information

requiring a modification to the REMS, and HCPs must have quick access to any new information.

- Minimize the burden on the HCP with regard to REMS.

CE providers may opt to develop REMS CE programs within a broader educational review of a particular disease state/condition and the use of the drug in overall management. Even so, it is critical that key information about the risk(s) that the REMS is intended to mitigate and REMS requirements are highlighted and made readily accessible to HCPs. Based on FDA's findings, to be effective, a CE program must be tailored to fit the learners' needs, but not every learner will need exposure to all of the broader educational content. FDA carefully considers the potential burden of a REMS on HCPs and on the health care delivery system. CE providers should also carefully consider the time and resources that will be needed for HCPs to effectively complete a CE program.

- Providing the CE activity in a variety of formats to increase accessibility to HCPs

There are a variety of formats that CE providers can use when developing and implementing a CE activity. Not all HCPs will have the time, and/or ability to attend and be located in proximity to live CE courses. Additionally, for those REMS that require HCPs to complete training to be able to prescribe or dispense the drug, it is imperative that the educational activity be readily accessible on a continuous basis (e.g., internet-based) so HCPs can access and complete the training in a timely manner.

- Developing a process for documenting completion of the REMS CE as well as linking the completion of the CE to the appropriate REMS requirements.

REMS that include ETASU that *require* HCPs to complete and document their training before being able to prescribe or dispense a drug may pose specific challenges. Additional content may need to be developed, for example, on how to successfully document program completion, become authorized to prescribe, and/or document CE completion. In some cases, CE providers and pharmaceutical companies will need to develop a process that separates the educational program focusing on risk messages and REMS requirements from the functional aspects of the REMS (i.e., a system that links the completed CE for the HCP to the company's REMS system to ensure all the REMS ETASU requirements are satisfied).

- Careful consideration should be given to all CE activities and how the activity will be assessed within the context of REMS assessments.

CE providers should consider how to incorporate more standardized training assessment methods that will provide information on both the effectiveness of CE activities on outcomes, as well as contribute to the overall assessment of the REMS, as stated in the REMS assessment plan.

IV. CONCLUSIONS

FDA carefully assessed the feasibility of developing a REMS that uses CE activities as a key component for provision of HCP education and training and for making it available both at the time of drug approval and after approval. These two contexts were discussed in detail with CE

accrediting bodies, the pharmaceutical industry, and other stakeholders to identify specific issues for consideration when undertaking CE development for individual REMS programs at different time points.

FDA determined that developing CE activities as part of a REMS with the initial approval of a drug would not be practical, because in some circumstances, the information and time needed for CE development could result in a delay in marketing of the drug. The postapproval setting appears more amenable to CE development in terms of timing and development of program content. CE activities could be included as a necessary component of an existing REMS, as part of a REMS modification, or during creation of a postapproval REMS.

Although FDA determined that developing CE activities as part of a REMS appears feasible in the postapproval setting, FDA acknowledges that any REMS requirement that is fulfilled through the development of CE programs creates special challenges that need to be considered and addressed by CE providers, pharmaceutical companies, and other stakeholders involved in the REMS CE development process. If CE is to be the primary tool to communicate the serious risk or the safe use conditions, additional guidance beyond labeling and the REMS will generally be needed (i.e. a FDA-developed Blueprint) to help ensure that CE providers include the risk messages, REMS requirements, and safe use conditions that are the subject of the REMS.

For REMS programs that require completion of training implemented through CE activities before prescribing or dispensing the drug, logistics will have to be designed and developed to ensure successful CE completion and documentation as well as efficient information flow of specific HCP information into a REMS database.

FDA welcomes the opportunity to work with pharmaceutical companies who wish to pursue incorporating CE into individual REMS.