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SPECIAL ARTICLE

Mitigating the Safety Risks of Drugs With a Focus on Opioids: Are Risk Evaluation and Mitigation Strategies the Answer?

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Abstract

Approximately 40% of all newly approved drugs are subject to safety restrictions inclusive of Risk Evaluation and Mitigation Strategies (REMS), which were created with the US Food and Drug Administration Amendments Act of 2007. This law expanded Food and Drug Administration (FDA) authority to require REMS of manufacturers but left implementation to the FDA. As a result, the potential access to medications that are effective but not without safety concerns has improved, yet the converse is also true because access may be restricted due to REMS requirements (eg, physician or patient registration). With the July 2012 reauthorization of the Prescription Drug User Fee Act, the FDA was given additional authorities and mandates for enhancing and modernizing the drug safety system—specifically, measuring the effectiveness of REMS as well as standardizing and better integrating REMS into the overall health care system. So, are REMS, which were conceived as a tool to improve medication safety, working? Specifically, are REMS achieving their intended outcomes (mitigating safety risks of effective drugs) without causing unintended consequences (creating a burden to the health care system and physicians and/or diminishing patient access to drugs)? Sitting squarely in the crosshairs, the approved shared REMS for extended-release/long-acting opioid analgesics provide a lens through which this question can be examined. This article discusses the current status, stakeholders, and key policy issues for clinicians with a focus on the shared REMS for opioids, as well as the anticipated role of clinicians in optimizing patient care in the new world of REMS.

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The US Food and Drug Administration (FDA) is responsible for protecting the public health by assuring the safety, efficacy, and security of human drug and biological products (among others) and for promoting the public health by helping to speed innovations that make medicines safer and more effective.[1] Ensuring that prescription drugs not only reach the market but are evaluated on an ongoing basis is not a new or novel concept. Today's Risk Evaluation and Mitigation Strategies (REMS), conceived as part of the Food and Drug Administration Amendments Act (FDAAA) of 2007, are simply the flavor du jour that has set the latest standard for ensuring a continued favorable benefit to risk profile for prescription drugs. The core issue is whether this latest attempt at mitigating safety risks has achieved its objectives or merely caused unintended consequences.

Prescription drug approval hinges on several key questions: Is the drug *efficacious* for the disease/syndrome/symptom it is intended to treat? Is the drug *safe* for use in the intended patient population? Do the *benefits* of the product outweigh the *risks*? How will those risks be managed, ie, through product labeling, pharmacovigilance efforts, REMS? While answering these questions is pivotal to initial approval, in today's world, the benefit to risk evaluation clearly happens throughout the life cycle of the drug, not just as a first step.

Risk Evaluation and Mitigation Strategies programs, enforceable, structured plans designed to manage specific risks associated with specific drugs, go beyond routine professional labeling. Clearly not all prescription drugs with a safety risk require REMS. Examples of the types of risks that REMS would aim to mitigate include serious infections (eg, progressive multifocal leukoencephalopathy), severe allergic reactions, liver damage, abnormal heart rhythms that can cause sudden death, or severe birth defects. When a REMS program

From ProEd Communications, Inc, Beachwood, OH.

is required, the safety measures developed are unique, and thus no two REMS are alike.[2]

Risk Evaluation and Mitigation Strategies can be mandated either during the approval process or postapproval on learning of serious risks with broader use and experience. The legal basis of the FDA's authority to mandate REMS stems from the FDAAA of 2007[3] as well as the Food and Drug Administration Safety and Innovation Act of 2012.[4] As a part of the Food and Drug Administration Safety and Innovation Act of 2012, the reauthorization of the Prescription Drug User Fee Act (PDUFA V) granted the FDA additional authorities and mandates for enhancing and modernizing the drug safety system. These mandates include measuring the effectiveness of REMS and standardizing and better integrating REMS into the overall health care system. The REMS legislation has provided the FDA with considerable and important powers to ensure drug safety, not only through the historic power of authority but also through the power of enforcement.[5] The FDA's broadened authority applies to any New Drug Application (NDA), Abbreviated NDA (ANDA), or Biologics License Application at any stage of the drug's life cycle. Ultimately, this new approach to risk management has further elevated the rigor that manufacturers must meet in postmarketing safety commitments.

Although the FDA stipulates the need for REMS, the pharmaceutical manufacturer (specifically the entity/license holder submitting an application, whether an NDA, ANDA, or Biologics License Application) is charged with developing the REMS program that it believes adequately mitigates the risks while effectively making the product available to those who need it. The FDA either approves or makes suggestions for revisions to the manufacturer's proposed REMS. Thus, the final REMS program is the result of an iterative negotiation process between the agency and the manufacturer. Risk Evaluation and Mitigation Strategies vary in scope and complexity depending on the magnitude of the risk to be mitigated. Common REMS elements are Medication Guides (MedGuides), Communication Plans, and Elements to Assure Safe Use (ETASU) (Table 1).[3]

As part of the REMS program, the manufacturer is required to submit assessments of the plan's effectiveness, typically at 18 months, 3 years, and 7 years. Failure to comply can mean the drug is considered misbranded, and associated penalties range from $250,000 to $1 million per violation and upwards of $10 million for continued violations.[6]

HISTORICAL PRECEDENCE

A typical drug's risks are communicated via the package insert and a patient package insert provided at the time of prescription dispensing. Depending on the physician and his office staff, risks may also be communicated at the time the prescription is written for the patient. Various issues have necessitated FDA action to improve the communication of the risk to benefit profile of drugs. Some of the earliest drivers of the need to initiate risk mitigation efforts were controlled substances inclusive of opioids, the quintessential being the Controlled Substances Act of 1970 that garnered the introduction of boxed warnings and "Dear Doctor" letters.[7] More recently, the opioids continue to drive this debate and were undoubtedly formative in the push toward REMS legislation—specifically, the misbranding charges brought against Purdue Pharma that were settled in May 2007 for $634 million in fines for fraudulently promoting OxyContin as less prone to

TABLE 1. Common Risk Evaluation and Mitigation Strategies Elements

Risk level	Element	Description
Lower	Medication Guide	Document written for patients highlighting important safety information about the drug; this document must be distributed by the pharmacist to every patient receiving the drug, whether the initial prescription or at each renewal
Escalating	Communication Plan	A plan to educate health care professionals on the safe and appropriate use of the drug; consists of tools and materials that will be disseminated to appropriate stakeholders
Highest	Elements to Assure Safe Use	Strictly controlled systems or requirements put into place to enforce appropriate use of a drug. They may include physician certification requirements to prescribe the drug, patient enrollment in a central registry, distribution of the drug restricted to certain specialty pharmacies
Highest	Implementation Plan	How certain Elements to Assure Safe Use will be implemented

Data from the Food and Drug Administration Amendments Act of 2007.[3]

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abuse with fewer narcotic adverse effects.[8-10] The lead-in to this case included increasing illicit availability and abuse of OxyContin nationwide, with a corresponding annual 18-fold increase of OxyContin prescriptions (approximately 5.8 million prescriptions in 2000) subsequent to the introduction of the drug in 1996.[11] Fast-forward to present day, with opioid pain relievers still the most widely misused and abused controlled prescription drugs leading to overdose (Figure).[12-15] Amid this backdrop is the most recent and highly controversial approval of Zohydro ER (single-entity hydrocodone) in October 2013. It is the first approval of an opioid to carry the updated labeling now required for all extended-release/long-acting (ER/LA) opioid analgesics (as of September 2013)[16,17] and will be subject to the new postmarketing study requirements to evaluate its serious risks, including the risk of abuse with long-term use (longer than 12 weeks).[16-18]

CURRENT STATUS

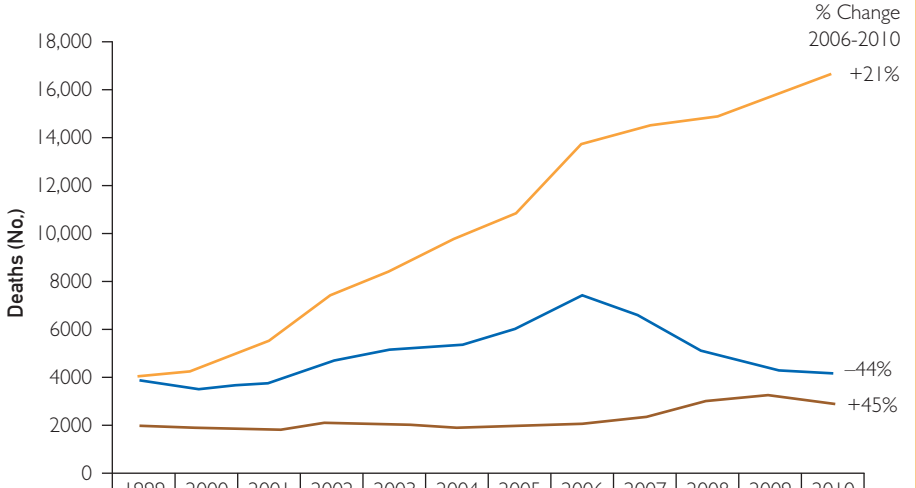
As of August 2014, more than 200 REMS have been approved for individual products since the FDAAA was signed into law in 2007; the FDA has since released 144.[19] Most of the released REMS appear to be MedGuide-only REMS, and their release appears to be related to the MedGuide draft guidance issued in November 2011 (see subsequent discussion in the section Are REMS Components Effective?).[20] At present, there are 68 approved REMS and 6 single shared systems REMS (ie, more than one drug follows the same REMS, including the Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy). It is anticipated that the number of REMS will continue to expand.[7]

RELEVANT POLICY ISSUES

It is clear that REMS are here to stay. It is also clear that current development and assessment processes need real-world input from frontline practitioners on numerous levels. The following are among the priority policy issues in play.

Administering REMS

The burden placed on the health care system, patients, physicians, and other health care professionals to administer the varied and growing number of REMS is an important issue. Key stakeholders (Table 2) recognize that the FDA must adequately balance the mitigation of a drug's risks



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Opioid analgesic	4030	4400	5528	7456	8517	9857	10,928	13,723	14,408	14,800	15,597	16,651
Cocaine	3822	3544	3833	4599	5199	5443	6208	7448	6512	5129	4350	4183
Heroin*	1963	1843	1784	2092	2084	1879	2010	2089	2402	3041	3279	3038

FIGURE. Overdose deaths involving opioid analgesics, cocaine, and heroin, United States, 1999-2010. Not all overdose deaths specify the drug(s) involved, and a death may involve more than one specific substance. The increase in 2005-2006 in opioid deaths is related to nonpharmaceutical fentanyl.[12] *Heroin includes opium. Data from the Centers for Disease Control and Prevention.[13]

TABLE 2. Key Stakeholders Affected by REMS

Pharmaceutical industry (the players)	The product manufacturer is solely responsible for REMS development, which can be resource-intensive because all appropriate parties (eg, manufacturer, specialty pharmacy, training resources) must be organized and legal responsibilities and liabilities must be delineated and submitted to the FDA for review and approval.[5] The manufacturer is also responsible for implementing and monitoring the REMS program, following the agreed on schedule. However, manufacturers are uncertain of what information the FDA wants or when and how to implement a REMS program. Further, ongoing assessment of the program is a lengthy process for the manufacturer and the pharmaceutical industry as a whole because there is little precedence or guidance.[21] Although fines are a legal enforcement mechanism, the FDA has not used them to any great extent to date. Risk Evaluation and Mitigation Strategies can have an impact on manufacturers' cash flow and can have a negative effect on the valuation of the drug as manufacturers incur additional costs of commercialization. Conversely, REMS can be leveraged as an opportunity for commercialization—because certain drugs would not be approved without one, by undertaking REMS, a manufacturer is able to offer a "risky" drug to patients and is then able to recoup development costs and make a profit. Manufacturers need to consider the impact of increased postapproval measures when developing a compound.[22]
Government (FDA, OIG, OSE; the enforcers)	The FDA holds regulatory authority to mandate that a manufacturer develop a REMs program. It has issued various guidances and conducted numerous open public hearings in support of REMS and shared REMS. Currently, the FDA's workload related to postmarketing drug safety has increased as a result of its new authorities and other factors. Although the agency has received increased funding and is hiring staff to conduct postmarketing drug safety activities, it faces difficulties in recruiting to meet its increasing responsibilities.[21] Industry observers note that limited resources also affect the FDA's ability to review REMS programs and any revisions, to develop policies for implementing postmarketing safety programs, and to answer manufacturers' questions.[21,23]
Health care professionals, institutions, health plans, pharmacies, wholesalers, distributers (the implementers)	As primary implementers of any given REMS program, these stakeholders as a group shoulder much of the burden. First, none of these stakeholders were initially consulted for either the need for REMS or as a typical part of the REMS development process, and thus numerous challenges have been created. Regarding health plans, Kaiser Permanente has been very vocal about wanting a seat at the REMS table to ensure appropriate access and that undue burden (and therefore costs) are not placed on health plan providers, healthcare professionals, and pharmacies.[21] Kaiser formally petitioned the FDA to open up the process for designing and approving REMS with ETASU, noting that "REMS with ETASU essentially creates a whole new class of drugs from the delivery system and costs perspectives."[25] Similarly, the American Society of Clinical Oncology "noted with growing concern the process by which REMS are imposed without input from the physician community."[24] REMS requirements, designed to provide better risk communication, can include physician and allied health care professional training and certification, use of specialty pharmacies, and patient registries, but each REMS program is unique. The need to accommodate multiple nonstandardized programs is then imposed on an already fragmented health care system that is not equipped to accept the varying requirements across numerous fronts, particularly IT infrastructure, coordination of care, and personnel.[26] Depending on design, REMS can lead to effectively barring most health plan providers and pharmacies from participation because of the needs for individual certification and distribution programs. Most importantly, the lack of program standardization, the growing number in general, and the use of extensive ETASU continue to increase the cost to administer REMS.
Patients (the ultimate benefactors/users)	Unintended consequences for patients include whether they can or cannot physically access the drugs they need or if their physician is unable or unwilling to prescribe a REMS drug. In either scenario, the patient can fail to receive a beneficial treatment. Concerns have also been raised regarding privacy protections of patient health information while promoting greater access to REMS information with electronic infrastructures.[25,27] Although patients clearly gain from having access to drugs that might not otherwise be available or theoretically safer access to "risky" drugs, it is as yet unclear if these benefits are being realized.

ETASU = Elements to Assure Safe Use; FDA = Food and Drug Administration; IT = information technology; OIG = Office of the Inspector General, US Department of Health and Human Services; OSE = Office of Surveillance and Epidemiology, FDA; REMS = Risk Evaluation and Mitigation Strategies.

in order to ultimately derive its benefits.[5,21-27] The challenge is the cumbersome nature of the workflow, patient access, education, and workload issues thrust upon these stakeholders as a result of current REMS programs. Key implementing stakeholders were not consulted on the design, rollout, or implementation of the initial REMS programs. Neither was forethought given to how these restrictive programs could/would be implemented into the existing fragmented health care infrastructure. These issues have led to a "snowball effect" on health care professionals and health systems. This problem is juxtaposed to recent legislation impacting these stakeholders: (1) PDUFA V has made REMS streamlining and integration a priority use of user fees for the 2013-2017 period and (2) the process of streamlining and integration could yield benefits in terms of cost savings (more shared REMS with greater cost sharing among manufacturers) or

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challenges in terms of cost additions (will health care professionals be able to seek reimbursement for their efforts from the pharmaceutical company?).

Are REMS Really Mitigating Risks?

The federally legislated assessment of REMS effectiveness is flawed because of inadequate manufacturer reporting and the FDA's limited ability for follow-up/review.[6,28,29] In its February 2013 report, the Office of the Inspector General of the Department of Health and Human Services found that only 14% of the REMS programs reviewed were actively meeting all of their goals to effectively mitigate risk.[6,28] The report ultimately made 7 recommendations for ways to administratively improve the REMS assessment and evaluation process. The FDA agreed with 6 of the recommendations but stopped short of supporting the recommendation to seek legal authority (through additional legislation) to enforce receiving the necessary follow-up information from pharmaceutical companies. The FDA noted that the evolving methodologies and statutory landscape of risk management are contributing to the challenge of determining whether REMS are achieving their intended outcomes.[28] Evaluation of REMS effectiveness is a key area of focus for the FDA that will require physicians and other health care professionals feedback as well as collaboration among manufacturers and other partners in REMS implementation.

Are REMS Components Effective?

A further issue is whether the REMS components (MedGuides, ETASU, and Communication Plans) are really effective and how the digital and social media fit into the equation. This issue is best summarized by a 2009 blog post from the Eye on FDA website: the FDA is a data-driven agency, yet it has not collected any data to document that the MedGuides (a key pillar of REMS) are effective.[30] Further, the blogger encouraged the FDA to use its technical sophistication to mine the metrics-rich data readily available in digital and social media and encouraged pharmaceutical companies to "lead the FDA to water" on the use of social media in risk management education, implementation, and assessment.[30] Since then, the FDA has held 2 open public hearings (in 2009 and 2011) that were well attended. In January 2014, the FDA released draft guidance on interactive promotional media, which although not exactly addressing the adverse event reporting conundrum does appear to clarify that manufacturers are not responsible for user-generated content over which they have no control. The clock is ticking, however, and although the full guidance was due to be released in July 2014, the most recent communications included a Social Media Guidance Webinar on July 10, 2014, that encompassed all 3 of the social media–related draft guidances.[31,32]

Single Shared or Classwide REMS Programs

The impact of and impetus for single shared or classwide REMS programs is another policy issue.[26,33] The first of these, for isotretinoin products, rolled out in October 2010. The largest is the ER/LA opioid analgesic shared REMS initially approved in July 2012. Previously, REMS tended to be designed for smaller populations of patients, but with the advent of ER/LA opioids, the reach of these high-risk drugs extends to a far greater number of patients. Single shared REMS are expected to become more common over time because they ease the burden on the entire health care system. Most notable is the single Web portal for accessing relevant REMS information and tools including MedGuides and prescribing information, as well as simplifying patient registries and other components that may be required by the REMS. Other important elements are easier access for health care professionals to administer the REMs and patient access facilitated by creation of a shared information resource typically via a Web portal.

REMS as a Legal Tool to Protect Manufacturers From Generic Competition

Brand-name pharmaceutical manufacturers have begun using REMS as a strategy to prevent generic companies from procuring product samples to conduct their required bioequivalence studies for ANDA applications.[34,35] The Federal Trade Commission and the Generic Pharmaceutical Association have approached the courts on this issue as one of several distribution restrictions being used by brand-name manufacturers to block the sale of product samples. Specifically, REMS programs often restrict distribution of drugs and may essentially block the legal commercial flow of drugs to wholesalers, the usual

source for samples by generic manufacturers. Brand-name manufacturers claim that they do not want to expose themselves to liability risks by providing large quantities of drug to a "third party" for testing under circumstances not under their control, for example.[36] Given that approximately 40% of all new drugs are currently subject to FDA-imposed safety restrictions including REMS, this restrictive access policy only fosters the ability of brand-name manufacturers to block generic competition.[35] The Generic Pharmaceutical Association predicts that the ANDA pathway will be "foreclosed" by these actions, thus limiting availability of generic versions of brand-name products with REMS. This prediction was recently validated, in part, by the release of a report conducted by Matrix Global Advisors indicating lost savings of upwards of $5.4 billion in spending on pharmaceuticals due to the delayed arrival of 40 potential generic drugs.[37]

REMS for ER/LA Opioid Products

Are REMS for ER/LA opioid products really part of the solution or an overreaction? The increasing rates of accidental overdose, abuse, and misuse, despite a multipronged effort inclusive of risk management strategies to stem the tide, served as the impetus for the FDA to engage in and develop a shared REMS program for all ER/LA opioid analgesics.[38] Interestingly, some have complained, and thus the continuing controversy, that the current ER/LA REMS do not encompass the short-acting versions of common ER/LA opioids and that these versions are more easily, and thus more frequently, prescribed and consequently have a higher prevalence of abuse.[39] One unintended consequence of this REMS program could be the shifting from opioids to other equally challenging (ie, due to adverse effects) classes of pain medications, such as nonsteroidal anti-inflammatory drugs and acetaminophen, by prescribers.[34]

MITIGATING THE SAFETY RISKS OF OPIOIDS

It is clear that the evolution of risk management has brought with it a number of issues. The remainder of this article will focus on one key policy matter that touches health care professionals everywhere: Will the ER/LA Opioid Analgesics Shared System REMS have an impact on opioid abuse, misuse, and accidental overdose while maintaining appropriate access for patients with a legitimate need? This represents a policy issue on its own as well as a surrogate for the current challenges of REMS overall.

Looking Through the Lens of the ER/LA Opioid Analgesics REMS

The ER/LA opioid analgesics shared system REMS program was approved by the FDA in July 2012. Discussions about this REMS program began in early 2009 when letters were sent to more than 20 manufacturers of more than 30 brand-name and generic drugs (NDAs and ANDAs) with active ingredients that included hydromorphone, fentanyl, morphine, methadone, oxycodone, and oxymorphone.[40,41] Published in the *Federal Register* on April 20, 2009, the ER/LA REMS announcement indicated that REMS would be required but that specifics would be determined via a collaborative effort among manufacturers, advocacy groups, pain and addiction associations, and the public. After much discussion at open public hearings on the topic, the FDA convened a joint meeting of its Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee in July 2010 to discuss the proposal for a classwide REMS program for ER/LA opioid analgesics. Although the committees agreed that education was fundamental to the proposed REMS, they believed that it should be mandatory for all opioids, not just the ER/LA opioids. Specifically, members felt that the public health concern was related to misuse and abuse of *all* opioids and as such warranted a universal approach to both extended- and immediate-release opioid preparations.[42] The committees universally agreed that the goals of the proposed REMS were appropriate but the individual elements were not sufficient to curb the current misuse and abuse seen with opioid preparations.[42] The final vote is the most telling: when asked whether they agreed with the FDA's proposed REMS for ER/LA opioid analgesics, committee members voted a resounding 25 "No" to 10 "Yes." The FDA took the committees' recommendations under advisement and ultimately decided that there was a disproportionate safety problem associated with the ER/LA opioid analgesics and that it was important to take a stepwise approach focusing first on education for prescribers of ER/LA opioid analgesics.[41]

Eventually released in July 2012, the stated goal for the shared ER/LA REMS is to reduce

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serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. The primary element is an education program for prescribers (eg, physicians, nurse practitioners, physician assistants) that can be found at the ER/LA Opioid Analgesics REMS website built specifically for this program.[43]

Through the Lens of Each Stakeholder: The Current Status

The FDA acknowledges that efforts to date have not curbed the nonmedical use of opioids and has taken the step to mandate REMS for all ER/LA opioids and rapid-onset opioids, ie, transmucosal immediate-release fentanyl (TIRF), but no other short-acting or immediate-release opioids. With regard to the ER/LA REMS, the FDA has provided a blueprint for prescriber-only education/training, but it has not mandated that prescribers partake, only that manufacturers must provide the training to all prescribers. The FDA has also mandated that manufacturers provide educational materials for patients. In contrast to the ER/LA REMS, the TIRF REMS program has many more requirements for all stakeholders (Table 3) despite being listed as having similar REMS components (ie, MedGuide, ETASU, and implementation system). Essentially, as mandated by the FDA, the TIRF REMS Access program requires pharmacies, prescribers, patients, and wholesalers to enroll in the REMS program in order to utilize TIRF medications. Specifically, the TIRF products outlined in Table 3 are available only through the TIRF REMS Access program, which is a restricted distribution program.

Manufacturers formed the REMS Program Companies (RPC) to tackle the implementation of the shared ER/LA opioid REMS. The RPC has taken the stance that the education/training is mandatory and has implemented an approach to provide this training by soliciting educational grants from continuing medical education/continuing education companies for the independent development of the certified education programs for opioid prescribers. The RPC has included pharmacists in this mandatory training; however, the FDA does not require this audience as part of the REMS program.[39] In addition, the RPC is establishing a computerized tracking program for the express purpose of prohibiting community and institutional pharmacies from ordering certain medications from designated wholesalers unless they are registered in the RPC REMS program.[39] Registration will be limited to those pharmacies with a designated pharmacist who completes the required educational programs.

Health care professionals have participated in this shared REMS development process along the way and/or expressed opinions of the shared REMS. A survey of primary care practitioners (87% of respondents) and specialists fielded in advance of the final ER/LA REMS indicated that 50% of the responding physicians would be willing to comply with the mandatory education component of the REMS—if it were no more than 2 hours including the requirement to provide education to patients. Importantly, many were not willing to prescribe opioids controlled by the new REMS if the requirements on them were more exhaustive.[44] This could have the unintended effect of decreasing access to these medications for legitimate medical purposes.

Numerous health care associations have provided comments and participated in open public hearings with the FDA on the ER/LA REMS including the American Society of Clinical Oncology, the American Society for Pain Management Nursing, the American Pharmacists Association, and the American Society of Health-System Pharmacists.[45-47] Stakeholders remained actively engaged in the more than 3-year development process, providing some hope that the process of collaborative development for shared REMS does at least appear to be workable.

The Bigger Picture

The overall economic consequences of this REMS program have not yet emerged, given that the first stage of prescriber education rolled out on March 1, 2013, and is being provided at no or nominal cost to prescribers. However, there are costs to the pharmaceutical companies involved in getting the shared REMS portal and education programming off the ground. The downstream social implications are whether deserving patients will be affected by the graduated rollout of the REMS education and access restrictions, which have the potential to limit where patients may obtain their prescriptions. However, the FDA does not

TABLE 3. Opioid REMS Key Attributes

	TIRF	ER/LA
Approval date	December 28, 2011	July 9, 2012
Most recent REMS modification	November 7, 2013	July 23, 2014
Resources	www.TIRFREMSaccess.com Phone: 1-866-822-1483 www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM289730.pdf	ER/LA Opioid Analgesics REMS website (www.ER-LA-opioidREMS.com)
Medication Guide	Yes	Yes
ETASU	Yes	Yes
Education/training	Yes, required	Yes, encouraged and voluntary, not required
Certification required to prescribe	Yes	No
Specific program components	• TIRF REMS Access Prescriber Program Overview • TIRF REMS Access Education Program • Knowledge Assessment • Prescriber Enrollment Form • Patient-Prescriber Agreement Form • TIRF REMS Access Patient and Caregiver Overview • Frequently Asked Questions • TIRF REMS Access website	• Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioid Analgesics • FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics • Prescriber Letter 1 • Prescriber Letter 2 • Prescriber Letter 3 • Professional Organization/ Licensing Board Letter 1 • Professional Organization/ Licensing Board Letter 2 • ER/LA Opioid Analgesics REMS website
Knowledge assessment	Required	Strongly encouraged review of ER/LA materials via ER/LA Opioid Analgesic REMS website www.er-la-opioidrems.com
Prescriber enrollment form	Required	NA
Patient-prescriber agreement form	• Required with each new patient before writing the patient's first prescription for a TIRF medicine, and agreement renewed every 2 y • Copies to patient and back to the Access program via website or fax	NA
Dispensing pharmacy certification required	• TIRF medicines will only be dispensed by pharmacies that are specially certified • Includes successful completion of the Knowledge Assessment and Pharmacy Enrollment Form	NA
Implementation system	Required	Not required
Wholesaler/distributor enrollment required	• Yes • Wholesalers/distributors must complete and sign the Distributor Enrollment Form • Includes staff training, distribution to only validated pharmacies, and reporting requirements • Incumbent on sponsor to ensure compliance by wholesalers/distributors	Not required

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TABLE 3. Continued

	TIRF	ER/LA
Sponsor database	TIRF sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (ie, active or inactive) and will monitor and evaluate implementation of the TIRF REMS Access program requirements	Not required
Timetable for submission of assessments	• TIRF NDA sponsors will submit REMS assessments to the FDA at 6 and 12 mo from the date of the initial REMS approval and annually thereafter • To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 d before the submission date for that assessment • TIRF NDA sponsors will submit each assessment so that it will be received by the FDA on or before the due date	REMS assessments will be submitted to the FDA at 6 and 12 mo after the initial approval date of the REMS (July 9, 2012) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 d before the submission date for that assessment. The NDA holders will submit each assessment so that it will be received by the FDA on or before the due date based on the initial approval date of the REMS
Products included	• Abstral (fentanyl sublingual tablets) • Actiq (fentanyl citrate oral transmucosal lozenge) • Fentora (fentanyl buccal tablet) • Lazanda (fentanyl nasal spray) • Onsolis (fentanyl buccal soluble film) • Subsys (fentanyl sublingual spray) • Approved generic equivalents of these products are also covered under this program	• Avinza (morphine sulfate ER capsules) • Butrans (buprenorphine transdermal system) • Dolophine (methadone hydrochloride tablets) • Duragesic (fentanyl transdermal system) • Embeda (morphine sulfate-naltrexone ER capsules) • Exalgo (hydromorphone hydrochloride ER tablets) • Kadian (morphine sulfate ER capsules) • Methadose (methadone hydrochloride tablets) • MS Contin (morphine sulfate CR tablets) • Nucynta ER (tapentadol hydrochloride ER tablets) • Opana ER (oxymorphone hydrochloride ER tablets) • OxyContin (oxycodone hydrochloride CR tablets) • Zohydro ER (hydrocodone bitartrate ER capsules) • Morphine sulfate ER capsules • Oxymorphone hydrochloride ER tablets • Fentanyl transdermal system • Morphine sulfate capsules • Methadone hydrochloride tablets • Morphine sulfate ER tablets • Methadone hydrochloride oral solution • Oxymorphone hydrochloride ER tablets • Methadone hydrochloride tablets

CR = controlled-release; ER = extended-release; ER/LA = extended-release/long-acting; ETASU = Elements to Assure Safe Use; FDA = Food and Drug Administration; NA = not applicable; NDA = New Drug Application; REMS = Risk Evaluation and Mitigation Strategies; TIRF = transmucosal immediate-release fentanyl.

anticipate a negative impact on patient access to pain medications.[41]

Finally, still others believe that policymakers striving to protect population health by ameliorating the adverse outcomes of nonmedical use of opioid analgesics inclusive of accidental overdose and exposure of children have not done enough with the current REMS. They cite how little evidence exists to document the effectiveness of REMS to date.[34] In turn, the latest action from the FDA, announced September 10, 2013, is the mandate for classwide safety labeling changes and new postmarketing study requirements for all ER/LA opioid analgesics intended to treat pain.[18] The goal is to use the primary means of communicating information about

approved uses for a drug, the prescribing information, to clearly identify which patients are candidates for ER/LA opioids. As such, the label is being updated to state that ER/LA opioid drugs should be reserved for use in patients for whom alternative treatment options (eg, nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or otherwise inadequate to provide sufficient management of pain. The labeling changes describe more clearly the risks and safety concerns associated with ER/LA opioids and will encourage better, more appropriate prescribing, monitoring, and patient counseling practices. In conjunction with the label changes, the FDA is requiring that manufacturers conduct additional longer-term clinical trials to obtain more scientific data on the benefits and risks of ER/LA opioids given over long periods.[48] Some specific goals will include assessing a variety of known serious risks, including misuse, abuse, addiction, overdose, and death, as well as the risks of development of increasing sensitivity to pain. Douglas Throckmorton, MD, deputy director for regulatory programs in the FDA's Center for Drug Evaluation and Research, has said, "This is not the first or last initiative, and we will continue supporting broader efforts to solve the serious public health problems associated with the misuse and abuse of opioids."[49]

A Word About Zohydro ER

An April 2013 poll by Research!America indicates that more than 50% of respondents regard opioid drug addiction as a major US health problem and believe that doctors should face limits on their prescribing abilities for addictive pain medications.[38] As noted earlier in this article, the introduction and marketing of OxyContin may well have initiated the spiral of opioid misuse and abuse. Current statistics for opioid analgesics, inclusive of OxyContin, continue to be alarming, as detailed in the Figure. Interestingly, although the original OxyContin product is no longer on the market (voluntarily removed by Purdue)[50,51] and has been replaced by a more abuse-deterrent formulation,[50] the October 2013 approval of Zohydro ER, the first single-entity hydrocodone product, has met with considerable scrutiny.[52] Despite an 11 to 2 vote against approval due to concerns over the sheer volume of hydrocodone and the potential for addiction noted by the FDA's own advisory committee, the agency approved Zohydro ER.[53] The approval of Zohydro illustrates the quintessential risk management equation of balancing access to effective pain medications, opioids in particular, for patients who genuinely need them while managing the risks associated with them. In the eyes of the FDA and various health care professionals, there is a genuine need for access to a product like Zohydro ER even with its inherent risks.[54] In the end, and most importantly, the FDA cannot address the necessary risk management strategies and efforts for opioids on its own: prescribers, dispensers, and patients need to actively participate to prevent nonmedical use of opioids.[34]

CONCLUSION

Clearly, the future and legacy of today's REMS programs are a work in progress. The most recent PDUFA V reauthorization has the greatest chance of pushing forward toward an improved REMS benefit to risk ratio. Collaboration across many stakeholders is the unprecedented need, and the system is responding with the collaborative participation in and ultimate approval of the classwide ER/LA opioid REMS, which represent a potential inspiration and model for how the FDA can improve the utility and impact of REMS for the betterment of the public health. Further hope is indicated by the recent FDA REMS Standardization and Evaluation public meeting. As that process continues to unfold, it will be important for frontline clinicians to be a part of the solution by engaging in policy initiatives being undertaken by general and specialty associations, engaging in the process for implementing REMS at their institution or office practice, responding to FDA requests for comments on future legislation, and ensuring that patients receive the right drug for their disease regardless of whether that drug requires REMS. By actively sharing health care professional perspectives, the patient-physician relationship can be enhanced so that the true promise of REMS can be realized for patients, the ultimate benefactors of safer medication use.

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Abbreviations and Acronyms: **ANDA** = Abbreviated New Drug Application; **ER/LA** = extended-release/long-acting; **ETASU** = Elements to Assure Safe Use; **FDA** = Food and Drug Administration; **FDAAA** = FDA Amendments Act; **MedGuides** = Medication Guides; **NDA** = New Drug Application; **PDUFA V** = Prescription Drug User Fee Act; **REMS** = Risk Evaluation and Mitigation Strategies; **RPC** = REMS Program Companies; **TIRF** = transmucosal immediate-release fentanyl

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