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REVIEW ARTICLE

Assuring Safety of Inherently Unsafe Medications: the FDA Risk Evaluation and Mitigation Strategies

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Abstract The decision to approve a drug for clinical use is based on an understanding of its benefits versus the risks. Although efficacy is generally understood at the time of submission to the FDA for approval, the risks are more difficult to assess. Both PubMed (from 2000 to 2012) and the FDA website (www.fda.gov) were searched using the search terms "risk evaluation and mitigation strategy" (REMS). Articles for review were selected by relevance to topic, and their references were searched as well for additional relevant resources. Since the search results were not expected to contain research studies, formal quality assessment and inclusion and exclusion criteria were not utilized resulting in a narrative review. Few directly relevant research studies exist, although supporting documents such as government reports were available. For effective drugs with unclear or concerning safety records, the FDA has the option of requiring a risk evaluation and mitigation strategy, which allows a systematic approach to track and assure safe medication use. Over 100 different medications are currently covered by REMS, and each REMS is developed individually based on the needs of the specific drug or class. Although likely associated with improvements in medication safety, the potential benefit, limitations, and consequences of REMS are not yet fully understood.

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The FDA remains the arbiter of the suitability of a drug intended for clinical use and to assure the availability of medications that are both effective and safe. Although efficacy and safety are paramount, neither of these is absolute, and both must be individually assessed within the context of the target patient population, the disease being treated, and the potential frequency of use. In practice, this is fluid, since medications may acquire new indications, be used off-label, and change formulation. Although the FDA is not permitted to regulate the practice of medicine, its powerful position adjudicating drug approvals results in a substantial indirect influence on patients, health-care providers, and pharmaceutical industry.

Under ideal circumstances, medications should be effective and carry no risks. Effectiveness is generally assessed through the FDA approval process, with most new medications providing marginal gains over existing therapy. Complete safety, however, violates the pharmacologic principle that at a certain dose (that varies among individuals), all drugs have toxic effects. Thus, the goal of drug therapy is to maximize the risk-benefit relationship of pharmacotherapy. Certain diseases, such as cancer, may require a greater tolerance of risk even with potentially limited efficacy. In contrast, medications for diseases of minor severity may be subject to a more intensive risk benefit scrutiny. When the proper balance of risk and benefit is not easily discernable, the FDA is faced with the decision of permitting marketing with the assumption that adverse outcomes will be recognized in the postmarketing phase, rather than withholding a potentially effective therapy. Unfortunately, once marketed, a drug is likely to be used in populations that differ from those used to obtain approval, by diverse clinicians, and with monitoring standards less than those utilized in the initial studies, further complicating the risk-benefit analysis.

The aim of this review is to use the history and changes over time to explain the current status of the medication safety process at FDA for medications with recognized safety risks.

Search Methods

A review of PubMed from 2000 to 2012 was performed, as was a search of the FDA website (www.fda.gov), using the search terms "risk evaluation and mitigation strategy" (REMS). The articles for review were selected by relevance to topic, and their references were searched as well for additional relevant resources. Since the search results were not expected to contain research studies, formal quality assessment and inclusion and exclusion criteria were not utilized, resulting in a narrative review.

One Hundred Years: the Birth and Evolution of the FDA

The FDA was created by the 1906 Pure Food and Drug Act, which led to further functional enhancement with passage of the Food, Drug, and Cosmetic Act in 1938. This latter act, in direct response to mass poisoning and death related to the inappropriate use of diethylene glycol as a diluent for the antibiotic sulfanilamide, set up the requirement for the submission of proof of safety to the FDA prior to marketing. Several amendments over the subsequent decades further established the regulatory role of FDA. The Kefauver-Harris Amendment in 1962 established the previously unnecessary requirement that new drugs be proven effective [1]. The 2002 reauthorization of Prescription Drug User Fee Act (PDUFA III) included the provision that the FDA can recommend risk management plans (RiskMAPs) for higher-risk drugs that are deemed sufficiently beneficial for approval but carry a substantial risk not amenable to control through product labeling. Guidance from the FDA included several "tools" such as targeted education and outreach, reminder systems, and performance-linked access systems [2]. However, development and implementation of RiskMAPs were voluntary, and the FDA was not empowered to require postmarketing studies, label changes, risk communication ("Dear Doctor" letters), or boxed warnings. However, postmarketing studies are complicated and expensive to undertake, and there has been a limited commitment to reliably complete these studies [3]. Since the details of the postmarketing study design are often the result of negotiation between the pharmaceutical company and FDA and not strictly by FDA design, compromises must be made that may limit the ability of the trial to determine the outcome in question. Development of such efforts may be agreed upon during negotiation with the drug sponsor, but the only recourse for FDA in the face of noncompliance was to mandate drug withdrawal from the market. Thus, although FDA wields considerable clout prior to marketing (study selection, approval), postmarketing authority was lacking.

The impact of several public health tragedies, including dexfenfluramine-associated valvulopathies and cyclooxygenase-2 inhibitor-related myocardial ischemia as well as the increasing complexity of pharmaceutical products, led the FDA in 2005 to undertake a series of steps to improve drug safety. In addition to creating the Drug Safety Oversight Board [4, 5], a group of advisors consisting of FDA and other federal officials, the FDA commissioned the Institute of Medicine (IOM) to make recommendations for improvement in the current system. The IOM report was published in 2006 and made wide-ranging recommendations [6]. The five areas of augmented regulatory authority suggested by the IOM included the following:

1. Clarify or strengthen existing postapproval authority
2. Improve the processes of "direct to consumer" advertising
3. Enhance enforcement tools for postmarketing fulfillment of commitment
4. Improve public and health-care provider awareness that FDA approval is not the final word on safety or efficacy
5. Establish milestones in a drug's life cycle to trigger comprehensive safety and efficacy review.

In 2007, the Food and Drug Administration Amendments Act (FDAAA) provided the FDA with several of these capabilities [7]. These included the ability to require, not just propose, postmarketing studies and the authority to mandate the implementation of a REMS for drugs with the potential for harm [7, 8]. FDA can require a REMS to be implemented at the time of original approval or implemented or modified postapproval if FDA obtains new safety information. In either case, the goal is to allow the use of a drug that carries risk perhaps significant enough to preclude approval without a REMS. Since the approval process requires a careful risk-benefit analysis, often with suboptimal data, the REMS provide added short-term reassurance that the risks of a drug will be identified and managed as soon as a substantial risk is appreciated.

The number of REMS has grown from 60 medications in 2009 to 101 in early 2012 [9, 10], and as of July 2013, there were 72. This includes six class-wide or shared REMSs, which cover a number of related medications. Approximately 200 REMSs in total have been approved since 2008. Approximately 30 medications had associated RiskMAPs prior to the conversion to the REMS program. REMS will likely continue to increase in number and become more refined as more is learned about their attributes and consequences. REMS, unlike RiskMAPs, are enforceable and may be accompanied by monetary fines and restricted drug utilization.

Anatomy of a Risk Evaluation and Mitigation Strategy

A REMS is composed of one or more of the following (in an increasing order of complexity):

1. A medication guide
2. A communication plan
3. Elements to assure safe use (ETASU)
4. An implementation plan for ETASU.

The FDA determines which drugs require a REMS by considering the estimated number of eligible patients, the seriousness of the disease or condition, the duration of treatment, as well as the expected benefit and severity of adverse effects, among other aspects. As of early 2012, the 101 REMSs consist of the following: 26 are medication guide-only REMS, 32 include a communication plan and a medication guide, and 35 include elements to assure safe use [10]. A timetable for assessment is compulsory, with a minimum specified assessment by 18 months and by 3 years and in the 7th year after REMS approval. This assessment is designed to evaluate whether the REMS is meeting its goals and whether changes are required.

Education

The majority of REMS contain only educational information for patients, generally through the development of a medication guide. The importance of education is indisputable, but it cannot be relied upon as the only strategy for providing safe medication use [11].

Medication Guides

Medication guides are issued in specific circumstances, such as when (1) certain information is necessary to prevent serious adverse effects, (2) patient decision making should be informed by knowledge about a known serious side effect with a product, and (3) patient adherence to directions for the use of a product are essential to its effectiveness [12]. A medication guide essentially contains a patient version of the professional product labeling and is required to be dispensed with each initial and subsequent prescription. Importantly, a generic drug must use a single shared medication guide with the parent drug or must obtain a waiver.

Medication guides have generally proven ineffective in educating patients about the risks of taking certain medications. Current medication guides are of little value to patients due to their high complexity and poor comprehensibility [13, 14], and those patients who read them had an overall lack of understanding of risks associated with the medications. In one study, the average length of the guide was over 1,900 words, which is four single-spaced typed pages, and the mean reading level was grades 10 to 11 (which is far above the recommended range for such material). Furthermore, in a survey of pharmacists, only 26 % correctly identified that medication guides should be provided with both initial and subsequent prescriptions [15]. Under certain circumstances, a medication guide may be specifically required in the inpatient setting [12], but if a medication guide exists, it must be distributed at the time of discharge if outpatient use will ensue.

Communication Plan

A communication plan, in which targeted safety information is delivered to health-care providers, may be required to encourage implementation or explain certain aspects of the REMS. Such a plan may include sending so-called Dear Doctor letters to health-care providers or disseminating risk information through professional medical societies.

Implementation System

Implementation of a REMS is often not specifically detailed and is generally left to the sponsor. However, FDA may require an implementation system to monitor and evaluate the accomplishment of ETASUs. For example, FDA may require certification of distributors to ensure that only patients who meet the requirement of the REMS are able to obtain the drug. This may be achieved through monitoring and audits by the sponsor to ensure compliance at subsequent points [16]. For example, transmucosal immediate-release fentanyl (TIRF) sponsors must maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e., active or inactive) and will monitor and evaluate implementation of the TIRF REMS program requirements.

ETASU

As risks associated with medication use increase, the tools needed to prevent adverse effects must become increasingly rigorous. ETASU may be considered when the risk-benefit relationship of the medication would not be acceptable without one, and when a less complicated REMS component is unlikely to be sufficiently protective [10] (see Table 1). These complex REMSs have one or more of three elements: (1) health-care providers are specially educated and/or certified, (2) facilities (e.g., pharmacies, practitioners) that distribute the drug are specially certified, and (3) the drug is only dispensed if there is documentation of safe use conditions. Registries or restricted distribution programs may also be utilized.

The common component of many REMSs with ETASU involves assuring that prescribers and/or pharmacists are properly trained to understand the potential risks associated with each medication. In general, these programs are developed by

Table 1 Examples of drugs with complex REMS (containing ETASU) classified by risk concern

	Medication (by brand name)	Risk/reason for REMS
Addiction	Abstral (fentanyl sublingual tablets)	Abuse, misuse, overdose, and addiction
	Butrans (buprenorphine transdermal system)	Abuse, misuse, overdose, and addiction
	Exalgo (hydromorphone hydrochloride)	Abuse, misuse, overdose and addiction
	Onsolis (fentanyl buccal soluble film)	Overdose, abuse, addiction, and serious complications due to medication errors
	OxyContin (oxycodone hydrochloride controlled-release)	Abuse, misuse, overdose, and addiction
	Suboxone (buprenorphine and naloxone)	Abuse, misuse, overdose, and addiction
	Xyrem (sodium oxybate, GHB)	Abuse, misuse, overdose, and addiction, along with serious CNS effects including respiratory depression
Fetal exposure	Accutane (isotretinoin)	Adverse fetal outcomes
	Letairis (ambrisentan)	Adverse fetal outcomes
	Revlimid (lenalidomide) and Thalomid (thalidomide)	Adverse fetal outcomes
Cardiac	Avandia family [Avandia, Avandamet, Avandaryl] (rosiglitazone)	Myocardial infarction
	Tikosyn (dofetilide)	Risk of induced arrhythmia
GI	Lotronex (alosetron hydrochloride)	Ischemic colitis and complications of constipation
Infection/allergic reaction	Lumizyme (alglucosidase alfa)	Life-threatening or severe allergic reactions and severe skin and systemic immune-mediated reactions
	Soliris (eculizumab)	Meningococcal infection (*Neisseria meningitidis*), other serious infections, and possible serious hemolysis post-discontinuation
Hematological	Mifeprex (mifepristone)	Excessive bleeding
	Nplate (romiplostim)	Changes in bone marrow reticulin formation and bone marrow fibrosis, worsened thrombocytopenia after cessation, thrombotic/thromboembolic complications, hematological malignancies, and progression of malignancy in patients with a preexisting hematological malignancy or myelodysplastic syndrome (MDS), and medication errors associated with serious outcomes
CNS	Sabril (vigabatrin)	Vision loss and increased risk of suicidal thoughts and behavior
	Zyprexa Relprevv (olanzapine)	Post-injection delirium/sedation syndrome (PDSS)
Cancer	Erythropoiesis-stimulating agents (ESA): Aranesp (darbepoetin alfa); Epogen and Procrit (epoetin alfa)	Risk of shortened overall survival and/or increased risk of tumor progression or recurrence (also increased risk of death from cardiovascular and thromboembolic reactions)
Other	Extraneal (icodextrin)	Drug-device interaction and the potential for falsely elevated blood glucose readings

drug manufacturers and approved by the FDA. Although these programs vary in rigor, prescribers and pharmacists are generally required to complete enrollment forms, acknowledging that they understand the risks associated with the medication. Additionally, prescribers may be required to enroll their patients in REMS programs and educate them about potential adverse effects. Prescribers may further be required to "demonstrate that they can diagnose the condition for which the drug is indicated as well as diagnose and treat potential adverse effects from the therapy." This effectively limits the use of the drug to prescribers with advanced training or certification; periodic recertification may be required.

Documentation of safe use conditions ensures that medication is only distributed to patients with proper evidence that the prescriber, the patient, and the dispenser are all appropriately enrolled in the REMS program. Documentation of safe use may also include the requirement for laboratory analysis such as pregnancy tests and liver enzyme tests or the need for patient counseling (see Table 2).

All of these elements of REMS exist to improve drug safety, although documentation of their effectiveness remains limited, and a comparative study to determine their effectiveness has not been performed. There is no apparent ethical or practical method to withhold drug safety information from a patient to determine if REMSs are reducing adverse outcomes. Baseline data on the number of patients presenting with adverse effects prior to REMS implementation do not exist for most drugs.

The risks of nonmedical use or adverse effects related to certain medications are serious enough that FDA requires special monitoring through a registry or special distribution systems. Given the complexity of these systems, few drugs

Table 2 Examples of elements to assure safe use

Element	Drugs	Requirement (examples)
Documentation of safe use	Alvimopan (Entereg)	Dispensed only at hospitals that perform bowel resections, no more than 15 doses per patient
	Isotretinoin (Accutane (off market) and generic)	Negative pregnancy test, two documented forms of contraception (iPLEDGE)
	Lenalidomide (Revlimid) and all thalidomide analogs	Negative pregnancy tests
	Vigabatrin (Sabril)	Baseline ophthalmologic assessment within 4 weeks then every 3 months after
Prescriber training and/or certification	Buprenorphine/naloxone (Suboxone)	Complete course and certification
	Fentanyl transmucosal (Actiq, Fentora, and several others)	Pharmacy check prescriber certification with a sponsor database
	Erythropoiesis-stimulating agents (ESA): Aranesp (darbepoetin alfa); Epogen and Procrit (epoetin alfa)	Provider and hospital designee must complete training (APPRISE Oncology Program)
Safety monitoring	Olanzapine long-acting injection (Zyprexa Relprevv) Clozapine (Clozaril)	Continuous observation for 3 h post-injection (olanzapine) Complete blood count (clozapine)
Registries	Isotretinoin (generic only) Vigabatrin (Sabril)	iPLEDGE program SHARE program
Restricted distribution	Oxybate (Xyrem) Vigabatrin (Sabril)	Distribution from single national pharmacy (Xyrem)

have been required to utilize either (see Table 2), and they are limited to very high-risk medications with relatively small patient populations.

Registries

Registries are cumbersome and costly but allow for tracking and monitoring of safety and effectiveness. The Isotretinoin Pregnancy Risk Management Program (iPLEDGE), established in 2006, contains a patient registry that requires physicians, patients, pharmacists, and wholesalers to be registered into a centralized database [17]. All patients, male and female, are required to agree to monthly questioning and monitoring. For women of childbearing potential, physicians are also required to document monthly negative pregnancy tests as well as the attestation of the use of two forms of contraception, prior to authorization of each new prescription. Prior to dispensing the medication, the pharmacist must receive a unique authorization code from the manufacturer that documents compliance by all parties. The centralized pregnancy registry tracks patients who become pregnant and the outcome of each reported pregnancy. Registration in iPLEDGE is increasing with over 22,000 prescribers and 71,700 patients registered. Interestingly, the brand name of isotretinoin product, Accutane, is no longer marketed, but the initial sponsor must still maintain the REMS.

One potential benefit of such intensive paperwork and tracking is that the effectiveness of the iPLEDGE program can be assessed. Data show that there has been a reduction in the number of pregnancies occurring during isotretinoin therapy [17]. The pregnancy prevention program established in 1988 was a voluntary system for patients and prescribers. With this system, 2.8 to 3.4 pregnancies occurred per 1,000 courses of treatment. In April 2000, the System to Manage Accutane Related Teratogenicity (SMART) program was launched requiring mandatory participation of physicians and patients, although compliance was not strictly verified. This decreased the rate of pregnancies to 2.1 from 2.3 pregnancies per 1,000 courses of treatment. The iPLEDGE program, which replaced SMART, further reduced the number of pregnancies to 1.3 pregnancies per 1,000 female users of the program. Although better, this may still be considered as an unacceptable risk.

Sodium oxybate (Xyrem) is used to treat cataplexy in patients diagnosed with narcolepsy. It is chemically identical to the street drug gamma-hydroxybutyrate (GHB) and carries serious potential for nonmedical use. The Xyrem Success Program utilizes enrollment and education of prescribers and patients along with documentation of safe use condition before filling a prescription. When this information is received and reviewed by the manufacturer, a 1-month supply is shipped directly to the patient via overnight delivery. The pharmacist and the physician are required to contact the patient to confirm delivery and ensure an understanding of the safe use conditions. The success of this program should be relatively easy to determine because there are few patients using this medication and those who do are tracked very carefully. Between September 2002, when the Xyrem Success Program was launched, and March 2005, 8,391 patients were registered to receive sodium oxybate. Postmarketing surveillance tracking the first 6 months of therapy in 695 participating patients showed that 67 % suffered no adverse effects [18].

The reported adverse effects included nausea, vomiting, headache, dizziness, somnolence, tremors, confusion, insomnia, depression, anxiety, and incontinence. However, at least 10 deaths related to Xyrem were identified on a routine FDA site inspection, suggesting that although the success surveillance system worked, the reporting requirement to FDA did not [19].

The Unique Circumstances of the Opioid REMS

Opioid prescribing has greatly escalated in the past decade due to expansion of use for the management of patients with moderate-to-severe pain. This rise in use has been accompanied by a concomitant rise in nonmedical use and adverse effects, including death. In 2008, over 14,000 deaths were related to the misuse of prescription medications, primarily opioids, surpassing the combined total of heroin and cocaine in lethality [20]. Particularly concerning for their contribution to the prescription medication morbidity epidemic are the long-acting (LA) and extended-release (ER) opioid analgesics. The FDA has mandated the development of a REMS for ER/LA opioid formulations based on their potential for nonmedical use (i.e., use without a medical indication) and overdose. This class-wide REMS, which includes prescriber and patient education programs, will replace a host of individual REMS programs that have been developed for each opioid in this category [21].

According to the ER/LA opioid REMS, sponsors of these products are required to provide resources to educate prescribers in the use of these medications. This voluntary training must cover patient selection, counseling in correct use and risk, and assessment for misuse, dependency, and addiction. Sponsors are also expected to develop factual, patient information, and medication guides that are non-promotional [22].

The appropriateness of these methods of accountability for training and for disseminating information has been questioned by some, including an FDA advisory committee [23, 24]. FDA expects that sponsors will provide educational grants to accredited continuing medical education (CME) providers to offer the training covered in the blueprint [22].

There is an expectation at FDA that 25 % of the over 300,000 ER/LA prescribers will be trained by the end of the 1st year following implementation (which began in March 2013) with additional annual benchmarks and surveys of comprehension stipulated [25]. However, the likelihood of accomplishing this goal remains unclear, and there need to be plans if these benchmarks are not met.

There is no practical mechanism to implement a registry or restricted distribution system on this massive scale. This would likely prove unduly burdensome to both the patient and the health care system, and some physicians have expressed concern about their ability to comply with this mandate. However, many states have implemented or are improving their prescription drug monitoring programs to help clinicians track prescribing and dispensing of these and other controlled substance [26].

Although there is no REMS for short-acting oral dosage forms of opioid analgesics, a class-wide REMS for TIRF was recently implemented (www.tirfremsaccess.com). As with the ER/LA opioids, this REMS replaced a multitude of related individual REMS, although in distinction, this program is mandatory for prescribers, pharmacies, distributors, and patients. Furthermore, a patient-prescriber agreement is required with TIRF and is optional under the ER/LA REMS. The impetus for this REMS is less about abuse of TIRF products, which has been relatively minor, and relates to the appropriate patient selection (opioid tolerant, breakthrough cancer pain), conversion between products, and accidental exposures in children.

Limitations of REMS

Prior to this mandate, the drug manufacturers crafted each REMS independently, resulting in slightly different versions of related programs, even for identical or closely related drugs. The lack of standardization makes it difficult to extend an existing REMS for a single drug to cover an entire class of drugs [9]. This was specifically addressed by the FDA in crafting the opioid ER/LA REMS, by meeting with stakeholders such as pharmaceutical representatives, health-care providers, the public, and its advisory committee as well as accepting public comments on the proposed REMS.

Other complicating factors include a lack of universally accepted definitions and thresholds. For most drugs, there is no explicit mechanism to determine an acceptable risk-benefit relationship. Even if specified, the illicit nature of the misuse of certain drugs (e.g., the opioids) contributes to the difficulty in measuring the effectiveness of the REMS.

FDA must ensure that increasing the burden on patients, physicians, and the health care system by implementing a REMS does not compromise patient care. For example, prescribers may avoid prescribing drugs with complicated REMS requirements for several reasons, such as the extra effort and documentation required, which may not be reimbursed by insurance carriers. This may result in the increased prescription of drugs that are outside of the REMS, the effects of which are not necessarily predictable. A recent study revealed that 13.4 % of physicians would no longer prescribe an opioid product if required to obtain 4–8 h of training and 2 h of continued medical education every 2 years. However, 48 % of physicians said that they would be willing to complete 2 h of training, and 50 % would be willing to encourage patient compliance and register patients every 6 months [27]. Another survey of primary care physicians revealed general support for

the enhanced monitoring of the opioid REMS, concern that they will be ineffective, and discomfort with the potential for decreased opioid prescribing. Only 8 % of physicians included in this study were very familiar with the REMS, suggesting that the results reflect personal sentiment and are not data or experience based [28].

Education of prescribers and standardization of REMS components may prevent a shift in prescribing practices. Additional research regarding optimization of the REMS development process may be helpful to garner support from prescribers and assist with compliance. Compliance with REMS by the sponsor may be enforced through a series of escalating monetary penalties, although the consequences of noncompliance by prescribers, dispensers, or patients are less clear.

REMS can be revised or withdrawn if postmarketing surveillance or other data confirm an acceptable risk-benefit balance. For example, a reformulation in 2008 for sacrosidase (Sucraid) required implementation of a restricted distribution REMS to monitor for serious allergic reactions. An evaluation of the data collected for 18 months revealed that there was no increase in adverse events, and the drug was released from its REMS requirements [10].

The success of the REMS programs in protecting patients and the public health is difficult to study.

Likely in part due to the FDA's previous lack of authority to require data submission, only 7 of 49 REMS requirements of the sponsor reviewed by the Office of the Inspector General were considered complete [29]. In 2011, FDA established the REMS Integration Initiative designed to comprehensively review their REMS and success. This program includes assessment of how FDA has used its REMS authority and whether improved REMS designs can better integrate the evolving health care system to impact patient safety without burdening an evolving health care system [30]. An important requirement included in the reauthorization of PDUFA V is the standardization of REMS design, tools, and terminology. FDA has already began to organize stakeholder involvement in the process through a series of meetings and workshops to identify best practices and to continuously improve REMS.

Future practical efforts and research may focus on the potential use of state-based or national prescription drug monitoring plans to track prescriptions for controlled substances. Expansion of electronic prescribing or the use of serially numbered prescriptions will ease data accumulation and categorization. Proactively involving all health-care providers at several points in the prescribing process will make implementing and altering existing REMS less complicated. The burden placed upon the health care system may be minimized by standardization of REMS components.

There is a public and health-care provider perception that FDA approval assures the safety and efficacy of a medication [31]. Since this is not accurate, prescribers must become more familiar with the REMS process as well as its limitations. An important role of the FDA is to educate patients, prescribers, and pharmacists about the efficacy and safety of a medication. Complicating this process is the insight that all medications carry inherent risks, and some of which are dose-, patient-, or disease-dependent or otherwise predictable (e.g., mechanism-based), while others are idiosyncratic or otherwise unpredictable (e.g., allergic). REMS therefore maintain a critical role in allowing medications that may have a benefit in selected populations to be marketed despite well-understood or poorly defined risks.

Conflict of Interest None

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