

REPORT 8 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-10)  
The Evolving Culture of Drug Safety in the United States: Risk Evaluation and Mitigation  
Strategies (REMS)  
(Reference Committee E)

EXECUTIVE SUMMARY

Objective: This report briefly reviews some important milestones and developments in the evolving nature of drug safety activities among the Food and Drug Administration (FDA), the industry it regulates, and physician prescribers. Recommendations are offered to help guide AMA policy and actions in this arena, especially pertaining to the proliferation of Risk Evaluation and Mitigation Strategies (REMS).

Methods: The discussion and recommendations in this report emanate from previous AMA comments and activities surrounding the evolution of risk communication and risk management strategies used by the FDA for prescription drug products over the last two decades, including REMS; a recent letter directed to the current FDA Commissioner Margaret Hamburg, MD, on REMS; as well as preliminary guidance offered on this issue by the National Comprehensive Cancer Network.

Results: A REMS is a risk management plan that uses risk minimization strategies beyond professional product labeling. A REMS can be required before approval if the FDA determines it is needed to ensure that the benefits of the drug outweigh its risks, or it can be required post-approval if new safety information emerges that also requires use of this approach to keep the drug on the market. A REMS can include: (1) Medication guide or patient package insert; (2) Communication plan for health care practitioners; and (3) Elements to assure safe use (ETASU). The latter include several general categories but generally involve some feature that limits prescription of a drug to a defined set of conditions, parameters, or requirements that must be satisfied. These elements are designed, implemented, monitored, and evaluated for effectiveness by the manufacturer. More than 100 prescription drugs currently have a REMS attached to their use.

Conclusion: While the FDA does not have the authority to regulate physicians, its decisions and actions on REMS and other risk management approaches affect the daily practice of medicine. Physicians are responsible for implementing certain aspects of REMS in their practices. The number of REMS with ETASU continues to increase, and it seems clear that such REMS have the potential to affect patient access. The lack of uniformity among ETASU and the possible competing or conflicting nature of ETASU are onerous administrative burdens physicians face at the same time they are obligated to meet other administrative and clinical requirements of private and public insurance companies, such as prior authorization, step therapy, obtaining off-formulary drugs through an appeals process for their patients, and supporting patient assistance programs. A multiplicity of REMS programs exists requiring separate informed consent forms, enrollment, certification, or attestation, and they are primarily paper-based, which contributes to further disruption in workflow and patient care.

REMS should be patient-centric with minimal effects on prescribers and patient access. It is essential that the FDA establish a process for physician and other stakeholder involvement early in the REMS development process, and the process itself should be more standardized. An urgent need also exists to assess the impact of ETASU on an already overburdened healthcare system and on patient access, particularly for those patients with serious or life-threatening illnesses or in underserved communities.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 8-A-10

Subject: The Evolving Culture of Drug Safety in the United States: Risk Evaluation and Mitigation Strategies (REMS)

Presented by: C. Alvin Head, MD, Chair

Referred to: Reference Committee E  
(Brooks F. Bock, MD, Chair)

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1 INTRODUCTION

2  
3 Increasingly over the last decade, attention has been devoted to the process for prescription drug  
4 and biologic approval, the marketing of new drugs, risk communication, postmarketing  
5 surveillance, physician-industry relationships, and efforts to improve the benefit/risk ratio of drug  
6 therapy. Concerns about the Food and Drug Administration's (FDA) ability to monitor and  
7 respond to emerging drug safety problems have made drug safety a major topic of discussion in the  
8 U.S. With passage of the 2007 FDA Amendments Act (FDAAA), the FDA was granted new  
9 authorities to mandate postmarketing studies for drugs, require changes in prescription drug  
10 labeling, and to establish risk evaluation and mitigation strategies (REMS) for certain new drugs  
11 and biologics as well as already marketed products if new safety information becomes available.<sup>1</sup>  
12 REMS are required in the FDA's view if such a strategy is necessary to ensure that the benefits of  
13 the drug outweigh its risks.

14  
15 The AMA supports a drug approval process that is based on a scientific appraisal of risks and  
16 benefits. For some drugs, REMS involve requirements that directly impact and increase  
17 administrative burdens for physician practices (so-called elements to assure safe use or ETASU),  
18 and that have the clear potential to reduce access for some patients. REMS should support  
19 physician decision-making and help promote safe prescribing without erecting additional barriers  
20 that prevent the delivery of appropriate quality care. The Council is concerned about the expanded  
21 use of ETASU as part of REMS and the process used to require, develop, approve, and monitor  
22 such elements, especially the exclusion of practicing clinicians from that process.

23  
24 Accordingly, this report briefly reviews some important milestones and developments in the  
25 evolving nature of drug safety activities among the FDA, the industry it regulates, and physicians  
26 who serve as the ultimate prescribers of prescription drug products. Recommendations are offered  
27 to help guide AMA policy and actions in this arena, especially pertaining to REMS. These  
28 recommendations and several discussion points in this report emanate from previous AMA  
29 comments and activities surrounding REMS, including a recent letter directed to the current FDA  
30 Commissioner Margaret Hamburg, MD, as well as preliminary guidance offered on this issue by  
31 the National Comprehensive Cancer Network.

## 1 IMPORTANT DEVELOPMENTS INFLUENCING THE CULTURE OF DRUG SAFETY

### 2 3 *The Learned Intermediary and Evolving Risk Management Schemes*

4  
5 Prior to 1990, the physician was viewed as the ultimate “learned intermediary” with respect to drug  
6 prescribing. Physicians interpreted the language (i.e., instructions for use, precautions and  
7 warnings including black box warnings, dosage, and administration) of the professional product  
8 labeling (package insert) and applied it to clinical decision-making on prescriptions for individual  
9 patients. An early example of professional product labeling that introduced new requirements on  
10 physicians (beyond guidance) was the approval and marketing of the antipsychotic drug clozapine.  
11 This drug represented a novel therapeutic advance in managing patients with treatment-resistant  
12 schizophrenia, but its use was associated with development of severe agranulocytosis and possibly  
13 death in 1-2% of patients treated with clozapine. To mitigate this risk, an elaborate system  
14 (Clozaril Patient Management System [CPMS]) was established that required registration of  
15 patients, physicians, and pharmacies and the completion of a white blood cell count in order to  
16 dispense the product on a weekly basis. Thus, physicians were required to order the test and  
17 confirm results in order to prescribe the drug. The frequency of required blood tests has been  
18 relaxed over time, and generic manufacturers must maintain their own registry and communicate  
19 with the Clozaril® National Non-Rechallenge Masterfile maintained by Novartis.<sup>2</sup>

20  
21 Other prominent examples of drugs with risk management activities that used restricted distribution  
22 schemes developed during this time frame were isotretinoin and thalidomide, both of which are  
23 highly teratogenic but clinically useful products. Approximately eight years after the CPMS was  
24 created, a major risk management plan was adopted for reintroducing thalidomide to the  
25 marketplace (System for Thalidomide Education and Prescribing Safety or STEPS).<sup>3</sup> The STEPS  
26 program includes restricted distribution; a national registry for prescribers, patients, and  
27 pharmacists; central authorization of prescriptions; a patient informed consent form and phone  
28 survey; and required pregnancy testing in women of childbearing potential. For isotretinoin, risk  
29 management approaches evolved from a warning on the product labeling with its approval in 1982  
30 through a series of progressively more restrictive risk management programs, culminating in the  
31 Isotretinoin Pregnancy Risk Management Program (iPLEDGE) in 2006.<sup>4</sup> This program requires  
32 registration in a database by patients, prescribers, pharmacies, and wholesalers; a single centralized  
33 program for all isotretinoin products; mandatory monthly pregnancy tests before authorization of  
34 each prescription; mandatory monthly education for patients; and a centralized pregnancy registry.  
35 Despite these rigorous requirements, approximately 1.3 pregnancies per 1,000 female users of  
36 isotretinoin continue to occur.

### 37 38 *Drug Safety Withdrawals*

39  
40 The implementation of special prescribing requirements and registries for clozapine, isotretinoin,  
41 and thalidomide occurred against a backdrop of the withdrawal of several FDA-approved drugs  
42 from the U.S. market by the sponsoring company for safety reasons from 1980-2005 (see Table 1).<sup>5</sup>  
43 Despite the institution of black box warnings, revisions in product labeling warnings and  
44 precautions, use of “Dear Doctor” letters, public health advisories, etc., prescribing practices were  
45 not sufficiently modified to reduce the risk of patient harm, thereby contributing to the decision to  
46 withdraw some of these drugs from the market (e.g., terfenadine, mibefranil, bromfenac,  
47 astemizole, cisapride). In other cases, emerging information on adverse reactions was serious  
48 enough that the drug became too dangerous to use, particularly when effective therapeutic  
49 alternates were available (e.g., benoxepifen, suprofen, encainide, temafloxin, rapacuronium). A  
50 growing belief that existing risk communication vehicles and practices were inadequate to change  
51 prescribing behavior, even for some drugs with serious side effects, was established.

1 *Emerging Safety Information, Transparency, and Risk vs Benefit Determinations*

2  
3 Although inherent weaknesses in the voluntary approach (MedWatch) for detecting novel safety  
4 signals for newly marketed drugs are well known, several high profile product safety recalls or  
5 emerging safety issues focused attention on an inability or reluctance of the industry and/or the  
6 FDA to appropriately acknowledge or grant sufficient weight to safety concerns. These included  
7 pulmonary hypertension and cardiac damage with dexfenfluramine; cardiovascular morbidity and  
8 mortality associated with cyclooxygenase type II inhibitors (rofecoxib, valdecoxib), suicidal  
9 ideation associated with the use of antidepressants (and later antiepileptic drugs), and increased  
10 myocardial ischemic events with rosiglitazone. In some quarters, the FDA was blamed for a “drug  
11 safety crisis.”

12  
13 These events led to the commissioning of a report from the Institute of Medicine in 2006 to assess  
14 the U.S. drug safety system.<sup>6,7</sup> The report offered a number of recommendations addressing the  
15 FDA’s organizational culture, regulatory authority, and communication with patients. Among the  
16 former was a recommendation to include safety experts as an integral part of the drug review  
17 process and regulation. Recommendations also addressed the need to improve the transparency of  
18 the drug review processes and for timely identification, confirmation, and communication of risks  
19 and benefits on prescription drug products in order to inform clinical decision-making. The report  
20 also emphasized that the FDA lacked a systematic approach for identifying possible pre-market  
21 drug safety problems and the authority to require high quality post marketing studies to address  
22 safety concerns. The FDA issued a formal response to the recommendations in the IOM Report  
23 and has instituted some changes.<sup>8,9</sup> A November 2009 report from the Government Accountability  
24 Office concluded that the FDA had made some progress in enhancing postmarket drug safety, but  
25 that additional actions were needed.<sup>10</sup>

26  
27 THE FORERUNNER TO REMS—RISK MINIMIZATION ACTION PLANS

28  
29 With clozapine, isotretinoin, and thalidomide as key examples of drugs that had restrictive drug  
30 management programs, the FDA and sponsors began developing risk management plans for new  
31 drugs that contained one or more features commonly referred to as “restricted distribution.”  
32 Passage of the 2002 Prescription Drug User Fee Act (PDUFA III) established a more formal  
33 framework for the FDA to seek so-called Risk Minimization Action Plans (or RiskMAPS) for  
34 certain drugs. Through a series of public meetings, workshops, and concept papers, the FDA  
35 established a Guidance for Industry on this topic.<sup>11</sup> Under this approach, sponsors *voluntarily*  
36 *agreed* to impose certain conditions on the use of drugs that were associated with known and  
37 dangerous adverse reactions. The Guidance established a “toolkit” for RiskMAPSs comprising:

- 38  
39 • *Targeted education and outreach* (e.g., Dear Doctor letters, training programs for practitioners  
40 or patients, CME programs, prominent notifications, patient package inserts, direct-to-  
41 consumer ads, disease management programs);  
42  
43 • *Reminder systems* (e.g., consent forms; training with testing/documentation of knowledge,  
44 enrollment in special data collection systems, limited number of doses, special labeling,  
45 attestation that safety measures have been satisfied); and,  
46  
47 • *Performance-linked access systems* (e.g., product access dependent on laboratory testing  
48 results or other documentation, prescription only by certified health care practitioners, product  
49 dispensing limited to pharmacies or practitioners that elect to be specially certified, product  
50 dispensing only to patients with evidence or other documentation of safe-use conditions.)

1 Importantly, in this Guidance, the FDA cautioned that in selecting and developing the best tools for  
2 RiskMAPS, the sponsor should “maintain [the] widest access while minimizing administrative  
3 burdens” and should “identify and seek input from key stakeholders.” Additionally, the Guidance  
4 states “communication of risks and benefits through product labeling is the cornerstone for risk  
5 management efforts for prescription drugs,” and that “RiskMAPS [should] be used judiciously to  
6 minimize risks without encumbering drug availability or otherwise interfering with the delivery of  
7 the product benefits to patients.”  
8

9 Ultimately, about 30 drugs had RiskMAPS attached to them when the FDA was granted authority  
10 to require REMS in 2007. With the passage of FDAAA 2007, the FDA was granted broad new  
11 authority to require drug sponsors to make certain safety-related labeling changes, conduct  
12 postmarketing studies and clinical trials, and develop and put in place REMS, all with the intention  
13 of better identifying and managing risks of drugs on the U.S. market.<sup>1</sup> Recently, the FDA  
14 announced a different approach to mitigate drug safety concerns (separate from REMS) termed the  
15 Safe Use Initiative.<sup>12</sup> As described, the Initiative, which is in the early stages of development, will  
16 attempt to engage various stakeholders in a collaborative fashion to identify specific candidate  
17 drugs, drug classes, or therapeutic situations that are associated with preventable harm and then  
18 design and implement strategies to recognize and mitigate specific risks.  
19

20 The remainder of this report focuses on REMS, their impact on practicing physicians, and  
21 recommendations for future consideration regarding REMS development and implementation.  
22

## 23 WHAT IS A REMS 24

25 A REMS is a risk management plan that uses risk minimization strategies beyond professional  
26 product labeling; it can be required before approval if the FDA determines a REMS is needed to  
27 ensure that the benefits of the drug outweigh the risks of the drug, or it can be required post-  
28 approval if new safety information emerges that also requires use of this approach to keep the drug  
29 on the market. In general, it builds upon previous experience with risk management programs,  
30 including RiskMAPs. Manufacturers are accountable for development of the REMS program,  
31 certification and education of physicians, collection of performance and outcomes data, and  
32 surveillance/assessment of program effectiveness.  
33

34 A REMS can include: (1) Medication guide or patient package insert; (2) Communication plan for  
35 health care practitioners; and (3) Elements to assure safe use.<sup>1</sup> As designed, REMS also include an  
36 implementation system, a sponsor’s plan to assess the performance of the REMS, and a timetable  
37 for assessment. Medication guides or patient package inserts are provided to the patient at the  
38 point of dispensing. These are distinct from the patient medication information (PMI) sheets or  
39 leaflets that are typically dispensed with other prescription drug products and that vary depending  
40 on the pharmacy and vendor used to create them.  
41

42 Medication guides are widely viewed as a poor solution to mitigating risk and/or promoting  
43 appropriate and safe drug use. They are written at a literacy level that is too high and are skewed to  
44 presenting risk information that may confuse patients or result in actual refusal to take needed  
45 medications. The entire PMI framework is under review, and the FDA has announced its interest  
46 in moving toward a “single document” solution to improve communication of both benefit and risk  
47 information to the patient in a manner that promotes understanding and improves adherence in an  
48 appropriate way.<sup>13</sup> At this point, however, Medication Guides are an integral component of  
49 virtually all REMS programs.

1 *Elements to Assure Safe Use (Restricted Distribution)*

2  
3 Elements to assure safe use include the following general categories.<sup>1</sup> They are not mutually  
4 exclusive and in fact considerable overlap may exist for individual products.

- 5  
6 • Physicians who prescribe the drug must be certified or undergo specialized training;  
7 • Retail pharmacies or other dispensers (specialty/central pharmacies) of the drug must be  
8 certified;  
9 • Dispensing/administering the drug is allowed only in limited healthcare settings (e.g., sites  
10 equipped to treat adverse reactions);  
11 • The drug can be dispensed/administered only with evidence of safe use conditions (e.g.,  
12 dispensing the drug only after qualifying laboratory test results);  
13 • Each patient using the drug is subject to certain monitoring (e.g., ongoing periodic monitoring  
14 or required observational period following drug administration); and  
15 • Prescribers, pharmacies, and/or treated patients must be enrolled in a registry.

16  
17 Currently, of greatest concern to physicians are those drugs with REMS that include ETASU  
18 (restricted distribution features). As of May 19, 2010, REMS had been approved for 110 products  
19 as follows:<sup>14,15</sup>

- 20  
21 • 73 REMS with Medication Guides only  
22 • 24 additional REMS included a Communication plan;  
23 • 13 REMS included ETASU (all of these also include a Medication Guide and Communication  
24 Plan).

25  
26 In addition, 16 drugs were approved with restricted distribution programs prior to FDAAA and  
27 creation of the REMS framework. Accordingly, these products were “deemed” via FDAAA to  
28 have a REMS. Two of these products (ambrisentan and bosentan) have subsequently fulfilled  
29 regulatory requirements to be moved from the “deemed” into the formal REMS class.<sup>16</sup> Essentially  
30 then, 26 drug and biologic products currently are prescribed under restricted distribution schemes.  
31 See Table 2 for a brief synopsis of newly approved REMS since FDAAA. Table 3 contains a list  
32 of deemed REMS that eventually will achieve REM status under the provisions of FDAAA.

33  
34 **AMA AND PHYSICIAN CONCERNS WITH REMS**

35  
36 The statutory language in FDAAA explicitly required that “ETASUs must be commensurate with  
37 the specific serious risks listed in the labeling and cannot be unduly burdensome on patient access  
38 to the drug, patients with serious or life-threatening diseases, or patients who have difficulty  
39 accessing healthcare.” Also, the statute provides that to “the extent practicable, [the element(s)]  
40 must conform with other elements for other drugs with similar serious risks and be designed to be  
41 compatible with established distribution procurement and dispensing systems for drugs.”

42  
43 The number of drugs covered by ETASU has expanded since the passage of FDAAA in 2007. It  
44 appears that the current process utilized to develop ETASU as well as the actual implementation  
45 may not be consistent with congressional intent or the express statutory language. During the  
46 FDAAA legislative process, the AMA had extensive discussions with congressional staff  
47 concerning the ETASU provision. The AMA was assured that the intent was simply to codify then  
48 existing FDA regulations concerning “restricted distribution” that had been promulgated from a  
49 general grant of authority. A major concern was that a significant increase in reliance on ETASU  
50 as part of REMS was not warranted and could present problems for patient care.

1 *Unintended Consequences*

2  
3 REMS with ETASU may have several unintended consequences, including: (1) perceived onerous  
4 burdens on physicians to prescribe the drug and reluctance to participate in the REMS program; (2)  
5 encouraging the prescribing of alternatives that may be less effective but are not subject to ETASU;  
6 (3) reduced access for some patients to medically necessary drugs; and (4) creating confusion and  
7 possible errors by physicians for whom a new ETASU represents yet another regulatory burden.  
8 While the possibility of confusion and administrative burden may be minimal for some practices at  
9 this time, as the FDA increases the number of products subject to ETASUs, this concern will grow.  
10 An additional concern is that expanded use of ETASU will be used as a tool to limit prescribing to  
11 only labeled indications and could reduce manufacturer investment in innovative but high risk  
12 drugs or drug classes.

13  
14 Several of the drugs currently subjected to ETASU have narrow indications or are used primarily in  
15 in-patient settings; however, several are used in oncology. A recent special forum hosted by the  
16 National Comprehensive Cancer Network (NCCN) explored the implications of REMS for the  
17 oncology community and offered a set of recommendations for discussion; a formal white paper is  
18 forthcoming. As part of the process, a survey was conducted involving health care practitioners  
19 within NCCN.<sup>17</sup>

20  
21 The survey confirmed that nearly 70% of physicians were “not familiar” or only “somewhat  
22 familiar” with REMS regulations and the different components of REMS. Approximately 50% of  
23 practitioners believe that REMS interfere with the provision of patient care, will drive utilization  
24 towards drugs without REMS, and will create or increase disparities in care. Of the six drugs with  
25 ETASU that commonly affect oncology practice, 6% (thalidomide) to 34% (fentanyl buccal soluble  
26 film) of physicians had no plans to register because of administrative burdens. With regard to  
27 general REMS requirements and their perceived impact on prescribing, 62% of physicians would  
28 use a drug with a Medication Guide requirement, 57% would take extra time to document a  
29 required drug safety discussion, and 58% would complete education and training prior to use of the  
30 drug; but only 41% would complete education/training, enroll patients in a safety registry, and  
31 complete 2 to 3 data collection forms per patient. Both the NCCN and a recent white paper offered  
32 by the American Pharmacists Association strongly urged the creation of a standardized REMS  
33 process and/or templates that could be used based on certain strata or categories of risk.<sup>4</sup> The  
34 existence of complex REMS that are not standardized and are program-specific contributes to  
35 inefficiencies in administrative processes necessary for their implementation.

36  
37 None of the new REMS with ETASU, and very few of the older RiskMAP programs have been  
38 retrospectively reviewed, so the science base on which to judge the effectiveness of ETASU is  
39 virtually nonexistent. Through the Drug Safety and Risk Management Advisory Committee, the  
40 FDA will annually evaluate one or more drugs with ETASU to assess if the elements actually  
41 assure safe use of the drug; are not unduly burdensome on patient access to the drug; and to the  
42 extent practicable, minimize the burden on the healthcare delivery system. Reviewing only one  
43 drug annually, however, is not sufficient to evaluate the merits of REMS with ETASU.

44  
45 The FDA’s 2009 Draft Guidance for Industry on REMS describes the statutory framework and  
46 how the FDA has been applying it to new REMS, but does not specify how manufacturers are to  
47 comply with the FDAAA provision that ETASU cannot be unduly burdensome on patient access to  
48 the drug, patients with serious or life-threatening diseases, or patients who have difficulty accessing  
49 healthcare.<sup>18</sup>

1 OPIOID REMS

2  
3 Looming on the horizon is a class-wide REMS for certain schedule II opioid products, including  
4 oral methadone, transdermal fentanyl, and extended release formulations. This would be by far the  
5 largest REMS required affecting at least 20 million patients annually. In contrast to the process  
6 that has been employed for individual drugs, there has been opportunity for stakeholder input into  
7 the design of opioid REMS. The AMA convened a meeting of interested medical specialty  
8 societies on this topic, and has participated in numerous meetings, hosted both by the FDA and the  
9 Industry Working Group formed to respond to this monumental directive.

10  
11 Of great concern to the AMA is that the opioid REMS is occurring at the intersection of a public  
12 health crisis of prescription drug diversion and misuse and existing barriers to the appropriate  
13 treatment of chronic pain, cancer pain, and suffering at end-of-life. Virtually all of the unintended  
14 consequences of REMS with ETASU noted above would be magnified with this program. This  
15 raises the question of what ETASU are appropriate to improve prescribing of these products and  
16 avoid exacerbation of patient suffering, as well as the metrics that are needed to both define and  
17 evaluate the success or failure of such a program.

18  
19 DISCUSSION

20  
21 While the FDA does not have the authority to regulate physicians, its decisions and actions on  
22 REMS and other risk management approaches affect the daily practice of medicine. Physicians are  
23 responsible for implementing certain aspects of REMS in their practices, and as the number of  
24 REMS with ETASU continues to increase, it seems clear that such REMS have the potential to  
25 affect patient access.

26  
27 The lack of uniformity among ETASU and the possible competing or conflicting nature of ETASU  
28 are onerous administrative burdens physicians face at the same time they are obligated to meet  
29 other administrative and clinical requirements of private and public insurance companies, such as  
30 prior authorization, step therapy, obtaining off-formulary drugs through an appeals process for their  
31 patients, and supporting patient assistance programs.

32  
33 To meet some REMS requirements, physicians must spend additional time on administrative tasks  
34 associated with registration, training and certification, and documentation. This detracts from the  
35 time that is needed for diagnosis, patient discussion, and the design and implementation of a  
36 treatment plan that is acceptable to the patient. Furthermore, the multiplicity of programs requiring  
37 separate informed consent forms, enrollment, certification, or attestation are primarily paper-based  
38 and have not evolved with the architecture of electronic medical records and *e*-prescribing, which  
39 contributes to further disruption in workflow and patient care. Therefore, it is essential that the  
40 FDA establish a process for physician and other stakeholder involvement early in the REMS  
41 development process.

42  
43 A substantial need exists for standardization of the REMS process. REMS should be patient-  
44 centric with minimal effects on prescribers and patient access. Methods and metrics to assess the  
45 impact of ETASU on clinical practice and on access, particularly to underserved communities,  
46 must be addressed in order to ensure compliance with FDAAA. Further, the FDA must  
47 acknowledge and consider the cumulative impacts of REMS with ETASU on an already  
48 overburdened healthcare system and the costs of such requirements as the Agency contemplates  
49 any future such programs.

1 RECOMMENDATIONS

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The Council on Science and Public Health recommends that the following statements be adopted and the remainder of this report be filed:

That our American Medical Association urge that:

1. The Food and Drug Administration (FDA) issue a final industry guidance on Risk Evaluation and Mitigation Strategies (REMS) with provisions that: (a) require sponsors to consult with impacted physician groups and other key stakeholders early in the process when developing REMS with elements to assure safe use (ETASU); (b) establish a process to allow for physician feedback regarding emerging issues with REMS requirements; (c) clearly specify that sponsors must assess the impact of ETASU on patient access and clinical practice, particularly in underserved areas or for patients with serious and life threatening conditions, and to make such assessments publicly available; and (d) conduct a long-term assessment of the prescribing patterns of drugs with REMS requirements. (Directive to Take Action)
2. The FDA ensure appropriate Advisory Committee review of proposed REMS with ETASU before they are finalized as part of the premarket review of New Drug Applications, and that the Drug Safety and Risk Management Advisory Committee fulfills this obligation for drugs that are already on the market and subject to REMS because of new safety information. (Directive to Take Action)
3. To the extent practicable, a process is established whereby the FDA and sponsors work toward standardizing procedures for certification and enrollment in REMS programs, and the common definitions and procedures for centralizing and standardizing REMS that rely on ETASU are developed. (New HOD Policy)
4. REMS-related documents intended for patients (e.g., Medication Guides, acknowledgment/consent forms) be tested for comprehension and be provided at the appropriate patient literacy level in a culturally competent manner. (New HOD Policy)

Fiscal Note: Less than \$500

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**TABLE 1. Drug Safety Withdrawals: 1980-2005**

<b>Generic (Brand) Name</b>	<b>Approved</b>	<b>Therapeutic Class</b>	<b>Toxicity</b>
Zomepirac (Zomax)	1980	NSAID	Sever allergic reaction
Benoxaprofen (Oraflex)	1982	NSAID	Hepatotoxicity
Nomifensine (Merital)	1984	Antidepressant	Hemolytic anemia
Suprofen (Suprol)	1985	NSAID	Renal toxicity
Terfenadine (Seldane)	1985	Antihistamine	QT prolongation
Encainide (Enkaid)	1986	Antiarrhythmic	Increased mortality
Astemizole (Hismanal)	1988	Antihistamine	QT prolongation
Temafloxin (Omniflox)	1992	Anti-infective	Allergy, hemolytic anemia; renal damage
Flosequinan (Manoplax)	1992	Vasodilator	Increased mortality
Cisapride (Propulsid)	1993	Gastrointestinal	QT prolongation
Bromfenac (Duract)	1997	NSAID	Hepatotoxicity
Mibefradil (Posicor)	1997	Antihypertensive	Drug metabolism interactions
Grepafloxacin (Raxar)	1997	Anti-infective	QT prolongation
Trovafloxacin* (Trovan)	1997	Anti-infective	Hepatotoxicity
Troglitazone (Rezulin)	1997	Antidiabetic	Hepatotoxicity
Cerivastatin (Baycol)	1997	Statin	Rhabdomyolysis
Rapacuronium (Raplon)	1999	Anesthetic	Severe bronchospasm
Rofecoxib (Vioxx)	1999	NSAID (Cox-2)	Increased risk of stroke and myocardial infarction
Alosetron* (Lotrenox)	2000	Gastrointestinal	Ischemic colitis
Valdecoxib (Bextra)	2001	NSAID (Cox-2)	Increased risk of stroke and myocardial infarction

\* Subsequently re-introduced to the market with restricted labeling

**Table 2. New REMS with Elements to Assure Safe Use**

<b>Drug/Biologic</b>	<b>Elements Required</b>	<b>Rationale</b>
<b>Aranesp (darbepoetin alfa)</b>	<b>Elements to assure safe use:</b> (1) Drug to be prescribed and dispensed only by certified healthcare providers in a private practice; (2) Drug to be prescribed only by certified practitioners in hospitals; (3) Drug may be dispensed only by certified hospitals; (4) Sponsor must ensure that certified hospitals and healthcare providers agree to only dispense the drug to patients that have signed a statement before a course of ESA therapy.	<b>New Safety Information:</b> Clinical studies provided evidence that some cancer patients who are treated with erythropoiesis stimulating agents (ESAs) may experience increased tumor growth rate, leading to premature death.
<b>Epogen/Procrit (epoetin alfa)</b>	<b>Elements to assure safe use:</b> (1) Drug to be prescribed and dispensed only by certified healthcare providers in a private practice; (2) Drug to be prescribed only by certified practitioners in hospitals; (3) Drug may be dispensed only by certified hospitals; (4) Sponsor must ensure that certified hospitals and healthcare providers agree to only dispense the drug to patients that have signed a statement before a course of ESA therapy.	<b>New Safety Information:</b> Clinical studies provided evidence that some cancer patients who are treated with erythropoiesis stimulating agents (ESAs) may experience increased tumor growth rate, leading to premature death.
<b>Nplate (romiplostim)</b>	<b>Elements to assure safe use:</b> (1) Drug to be prescribed only by certified healthcare providers; (2) Drug to be dispensed only by specially certified practitioners and healthcare settings; (3) Patients treated with the drug must be enrolled in Nplate NEXUS program for documentation of safe-use conditions; and (4) Patients treated with the drug to be subject to certain monitoring.	<b>Identified Risk:</b> Bone marrow fibrosis, worsened thrombocytopenia after cessation of the drug, thromboembolic complications, increased risk of hematological malignancies and progression of malignancy in patients with pre-existing hematological malignancy or myelodysplastic syndrome, and serious complications due to medical error.
<b>Onsolis (fentanyl buccal soluble film)</b>	<b>Elements to assure safe use:</b> (1) Drug to be prescribed only by FOCUS enrolled healthcare providers; (2) Drug to be dispensed only by FOCUS enrolled pharmacies; (3) Patients treated with the drug must be opioid tolerant and enrolled in the FOCUS Program; (4) Patients receive a FOCUS counseling call with the initial prescription; (5) Drug must only be dispensed via a courier to patient's home; and (6) Pharmacies must have a Call Center for all pharmacist-patient interactions.	<b>Identified Risk:</b> Fentanyl is subject to abuse and misuse. In addition, use of this drug by patients who are not opioid tolerant can lead to overdose, sudden serious breathing difficulties and death.
<b>Zyprexa Relprevv (olanzapine)</b>	<b>Elements to assure safe use:</b> (1) Dispensed only by certified pharmacies; (2) Prescribed only by certified physicians; (3) Patient Care Program Registry.	<b>Identified Risk:</b> Serious complications related to post-injection delirium/sedation syndrome (PDSS) are associated with the use of this product.

<b>Sabril (vigabatrin)</b>	<b>Elements to assure safe use:</b> (1) <i>Mandatory registration of physicians and patients into the controlled distribution program, SHARE ; (2) Mandatory benefit-risk assessment prior to beginning of maintenance treatment; and (3) Visual testing reminder system.</i>	<b>Identified Risk:</b> vigabatrin-induced peripheral visual field defect (loss of vision) and suicidal thoughts and behaviors.
<b>Entereg (alvimopan)</b>	<b>Elements to assure safe use:</b> (1) <i>Drug to be dispensed in hospitals only; (2) Drug to be dispensed only in specially certified hospitals; and (3) Drug to be dispensed only to patients with evidence of safe-use conditions.</i>	<b>Identified Risk:</b> Serious risk of myocardial infarctions.
<b>Sucraid (sacrosidase)</b>	<b>Elements to assure safe use:</b> (1) <i>Drug to be dispensed from a single central pharmacy; (2) Drug to be dispensed only by healthcare providers who have particular training or experience; (3) Drug to be dispensed only to patients with documentation of safe use conditions; and (4) patients (or their caregivers) will be requested to complete a questionnaire about their experience using the new product versus their prior experience due to a change in the manufacturing process</i>	<b>New Safety Information:</b> Sucraid may contain the enzyme papain that is known to cause allergic reactions in some people. FDA cannot exclude the possibility of papain contamination.
<b>Exalgo (hydromorphone HCl) XR</b>	<b>Elements to assure safe use:</b> (1) <i>Drug to be prescribed only by healthcare providers who have training as to the potential risks and the safe use of Exalgo.</i>	<b>Identified Risk:</b> Modified-release opioids are subject to abuse and misuse. In addition, use of this drug by patients who are not opioid tolerant can lead to overdose, sudden serious breathing difficulties and death.
<b>Letairis (ambrisentan)</b>	<b>Elements to assure safe use:</b> (1) <i>Drug to be prescribed by specially certified healthcare providers; (2) Drug to be dispensed only by specially certified pharmacies and healthcare settings; (3) Patients treated with the drug must be enrolled in Letairis REMS program for documentation of safe-use conditions and re-enrolled annually; and (4) Patients treated with the drug to be subject to certain monitoring.</i>	<b>Identified Risk:</b> Serious risk of hepatotoxicity and teratogenicity when using ambrisentan.
<b>Oxycontin (oxycodone HCl Controlled Release)</b>	<b>Elements to assure safe use:</b> (1) <i>Drug to be prescribed only by healthcare providers who have training as to the potential risks and the safe use of Oxycontin.</i>	<b>Identified Risk:</b> Modified-release opioids are subject to abuse and misuse. In addition, use of this drug by patients who are not opioid tolerant can lead to overdose, sudden serious breathing difficulties and death.

<p><b>Promacta (eltrombopag)</b></p>	<p><b>Elements to assure safe use:</b> <i>(1) Drug to be prescribed by specially certified healthcare providers; (2) Drug to be dispensed only by specially certified pharmacies and healthcare settings; (3) Patients treated with the drug must be enrolled in Promacta CARES program for documentation of safe-use conditions; and (4) Patients treated with the drug to be subject to certain monitoring.</i></p>	<p><b>Identified Risk:</b> Hepatoxicity, bone marrow fibrosis, worsened thrombocytopenia and increased risk for hemorrhage after Promacta Tablets cessation, thromboembolic complications, an increased risk of hematological malignancies, and progression of malignancy in patients with a pre-existing hematological malignancy or in myelodysplastic syndrome (MDS).</p>
<p><b>Tracleer (bosentan)</b></p>	<p><b>Elements to assure safe use:</b> <i>(1) Drug to be prescribed by specially certified healthcare providers and pharmacies; (2) Patients treated with the drug must be enrolled in Tracleer Access Program (TAP) for documentation of safe-use conditions and re-enrolled annually; (3) Patients will have pretreatment liver function tests and monthly liver tests; and (4) female patients of child bearing potential will have pretreatment pregnancy test and monthly pregnancy tests thereafter.</i></p>	<p><b>Identified Risk:</b> Serious risk of hepatotoxicity and teratogenicity when using Tracleer.</p>

Appendix 1

List of Products with ETASU Deemed to Have in Effect Approved REMS

- Abarelx
- Alosetron
- Clozapine
- Dofetilide
- Eculizumab
- Fentanyl PCA
- Fentanyl citrate
- Isotretinoin
- Lenalidomide
- Mifepristone
- Natalizumab
- Small pox (Vaccinia) Vaccine, Live
- Sodium oxybate
- Thalidomide