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)

INTRODUCTION

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

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

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

Action of the AMA House of Delegates 2010 Annual Meeting: Council on Science and Public Health Report 8 Recommendations Adopted, and Remainder of Report Filed.

IMPORTANT DEVELOPMENTS INFLUENCING THE CULTURE OF DRUG SAFETY

The Learned Intermediary and Evolving Risk Management Schemes

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

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

Drug Safety Withdrawals

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

Emerging Safety Information, Transparency, and Risk vs Benefit Determinations

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

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

THE FORERUNNER TO REMS—RISK MINIMIZATION ACTION PLANS

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

- *Targeted education and outreach* (e.g., Dear Doctor letters, training programs for practitioners or patients, CME programs, prominent notifications, patient package inserts, direct-to-consumer ads, disease management programs);

- *Reminder systems* (e.g., consent forms; training with testing/documentation of knowledge, enrollment in special data collection systems, limited number of doses, special labeling, attestation that safety measures have been satisfied); and,

- *Performance-linked access systems* (e.g., product access dependent on laboratory testing results or other documentation, prescription only by certified health care practitioners, product dispensing limited to pharmacies or practitioners that elect to be specially certified, product dispensing only to patients with evidence or other documentation of safe-use conditions.)

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

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

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

WHAT IS A REMS

A REMS is a risk management plan that uses risk minimization strategies beyond professional product labeling; it can be required before approval if the FDA determines a REMS is needed to ensure that the benefits of the drug outweigh the risks of the drug, 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. In general, it builds upon previous experience with risk management programs, including RiskMAPs. Manufacturers are accountable for development of the REMS program, certification and education of physicians, collection of performance and outcomes data, and surveillance/assessment of program effectiveness.

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.[1] As designed, REMS also include an implementation system, a sponsor's plan to assess the performance of the REMS, and a timetable for assessment. Medication guides or patient package inserts are provided to the patient at the point of dispensing. These are distinct from the patient medication information (PMI) sheets or leaflets that are typically dispensed with other prescription drug products and that vary depending on the pharmacy and vendor used to create them.

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

Elements to Assure Safe Use (Restricted Distribution)

Elements to assure safe use include the following general categories.[1] They are not mutually exclusive and in fact considerable overlap may exist for individual products.

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

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

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

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

AMA AND PHYSICIAN CONCERNS WITH REMS

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

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

Unintended Consequences

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

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

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

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

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

OPIOID REMS

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

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

DISCUSSION

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, and as the number of REMS with ETASU continues to increase, 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.

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

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

RECOMMENDATIONS

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

Generic (Brand) Name	Approved	Therapeutic Class	Toxicity
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	Antiarrythmic	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

Drug/Biologic	Elements Required	Rationale
Aranesp (darbepoetin alfa)	**Elements to assure safe use:** *(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.*	**New Safety Information:** Clinical studies provided evidence that some cancer patients who are treated with erythropoeisis stimulating agents (ESAs) may experience increased tumor growth rate, leading to premature death.
Epogen/Procrit (epoetin alfa)	**Elements to assure safe use:** *(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 patiens that have signed a statement before a course of ESA therapy.*	**New Safety Information:** Clinical studies provided evidence that some cancer patients who are treated with erythropoeisis stimulating agents (ESAs) may experience increased tumor growth rate, leading to premature death.
Nplate (romiplostim)	**Elements to assure safe use:** *(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.*	**Identified Risk:** 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.
Onsolis (fentanyl buccal soluble film)	▪ **Elements to assure safe use:** *(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.*	**Identified Risk:** 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.
Zyprexa Relprevv (olanzapine)	**Elements to assure safe use:** *(1) Dispensed only by certified pharmacies; (2) Prescribed only by certified physicians; (3) Patient Care Program Registry.*	**Identified Risk:** Serious complications related to post-injection delirium/sedation syndrome (PDSS) are associated with the use of this product.

Sabril (vigabatrin)	**Elements to assure safe use:** *(1) 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.*	**Identified Risk:** vigabatrin-induced peripheral visual field defect (loss of vision) and suicidal thoughts and behaviors.
Entereg (alvimopan)	**Elements to assure safe use:** *(1) 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.*	**Identified Risk:** Serious risk of myocardial infarctions.
Sucraid (sacrosidase)	**Elements to assure safe use:** *(1) 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*	**New Safety Information:** Sucraid may contain the enzyme papain that is known to cause allergic reactions in some people. FDA cannot exclude the possibility of papain contamination.
Exalgo (hydromorphone HCl) XR	**Elements to assure safe use:** *(1) Drug to be prescribed only by healthcare providers who have training as to the potential risks and the safe use of Exalgo.*	**Identified Risk:** 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.
Letairis (ambrisentan)	**Elements to assure safe use:** *(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 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.*	**Identified Risk:** Serious risk of hepatotoxicity and teratogenicity when using ambrisentan.
Oxycontin (oxycodone HCl Controlled Release)	**Elements to assure safe use:** *(1) Drug to be prescribed only by healthcare providers who have training as to the potential risks and the safe use of Oxycontin.*	**Identified Risk:** 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.

Promacta (eltrombopag)	**Elements to assure safe use:** *(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.*	**Identified Risk:** 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).
Tracleer (bosentan)	**Elements to assure safe use:** *(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.*	**Identified Risk:** Serious risk of hepatotoxicity and teratogenecity when using Tracleer.

Appendix 1

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

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