Characterization of Current Risk Evaluation and Mitigation Strategies

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BACKGROUND

Under the United States (US) Food and Drug Administration (FDA) Amendments Act of 2007,[1] the FDA has enhanced responsibilities and authority with regard to pre- and postmarketing drug safety, including the authority to require a risk evaluation and mitigation strategy (REMS) for certain drugs in order to ensure that a drug's benefits outweigh its risks.

The FDA considers the following when determining whether to require a REMS for a particular drug:

- Estimated size of the population likely to use the drug involved
- Seriousness of the disease or condition that is to be treated with the drug
- Expected benefit of the drug with respect to such disease or condition
- Expected or actual duration of treatment with the drug
- Seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
- Whether the drug is a new molecular entity.

Elements of REMS may include one or more of the following components:

- Medication guide for patients
- Communication plan for health care providers, which may include the following:
  - Sending letters to health care providers
  - Disseminating information about the elements of the REMS to encourage implementation by health care providers or to explain certain safety protocols (e.g., medical monitoring by periodic laboratory tests)
  - Disseminating information to health care providers through professional societies about any serious risks of the drug and any protocol to assure safe use
- Elements to assure safe use (ETASU), which may include one or more of the following:
  - Health care providers who prescribe the drug have particular training, experience, or special certification
  - Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
  - Drug is dispensed to patients only in certain health care settings (e.g., hospitals)
  - Drug is dispensed to patients with evidence or other documentation of safe-use conditions (e.g., laboratory test results)
  - Each patient using the drug is subject to certain monitoring
  - Each patient using the drug is enrolled in a registry
- Implementation system, which may require the sponsor to complete the following tasks:
  - Monitor and evaluate implementation of ETASU by health care providers, pharmacists, and other parties in the health care system who are responsible for implementing such elements
  - Work to improve implementation of these elements.

Currently approximately 33% of all new molecular entities approved since 2008 have an approved REMS.[2]

OBJECTIVE

To review characteristics of approved and deemed REMS with ETASU in the US.

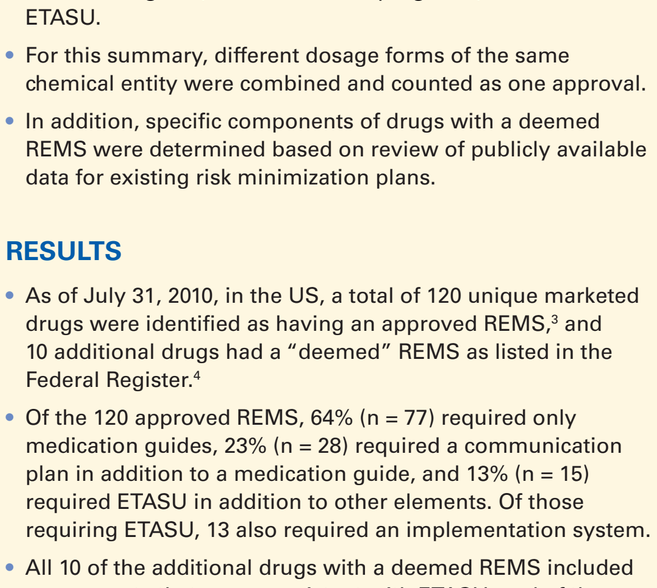
METHODS

- For the ISPE abstract, we identified all drugs recognized by the FDA as having an active REMS as of December 31, 2009. To provide the most up-to-date information in this rapidly changing regulatory environment, we included REMS approved through July 31, 2010 in the results for the poster.
- We reviewed publicly available information (e.g., www.fda.gov,[3] published articles, and product labels) to identify the safety issue prompting the REMS; the original indication for the products; the nature of REMS elements, including medication guide, communication programs, and details of ETASU.
- For this summary, different dosage forms of the same chemical entity were combined and counted as one approval.
- In addition, specific components of drugs with a deemed REMS were determined based on review of publicly available data for existing risk minimization plans.

RESULTS

- As of July 31, 2010, in the US, a total of 120 unique marketed drugs were identified as having an approved REMS,[3] and 10 additional drugs had a "deemed" REMS as listed in the Federal Register.[4]
- Of the 120 approved REMS, 64% (n = 77) required only medication guides, 23% (n = 28) required a communication plan in addition to a medication guide, and 13% (n = 15) required ETASU in addition to other elements. Of those requiring ETASU, 13 also required an implementation system.
- All 10 of the additional drugs with a deemed REMS included components that were consistent with ETASU, and of these, 2 had an implementation system. Six compounds that were also included in the Federal Register as having a deemed REMS were excluded from this summary (one was a vaccine, two were not available in the US at time of deemed REMS, and three had REMS approved since 2008 and were included in the "approved" REMS summary).
- Figure 1 shows the trend in REMS components over time since the first REMS were deemed in March 2008.

Figure 1. Trend in REMS 2008 to Present



[a] As deemed per Federal Register. Excludes small pox vaccine; Plenaxis and Ionsys (not available in US); Letairis, Tracleer, and Soliris, which now have approved REMS.

Table 1 provides a summary of the drugs with ETASU, as well as their approved indication, primary goal for the approved or deemed REMS, and the breakdown of elements of ETASU for each drug. Of drugs with ETASU:

- 24 require prescribers to have certain training or special certification
- 18 require pharmacies and other health care provides to have special certification
- 3 restrict drug distribution to patients only in certain health care settings (e.g., hospitals)
- 18 require evidence of safe use conditions
- 10 require special monitoring of patients
- 4 require patients to enroll in a registry
- 15 have implementation system to monitor and evaluate implementation of ETASU or to improve implementation.

Figures 2 and 3 show the distribution of REMS with ETASU by indication and the primary safety concern that prompted the REMS.

- Most of the drugs with ETASU fell into the biologic/immunologic/hematologic or central nervous system (CNS)/opioid categories.
- The primary safety concerns for drugs with ETASU were abuse potential and birth defects.

Figure 2. Distribution of REMS With ETASU by Primary Indication Category

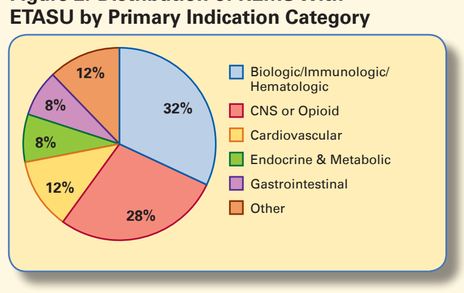


Figure 3. Distribution of REMS With ETASU by Primary Safety Concern

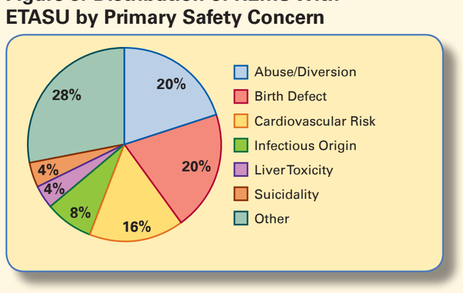


Table 1. Drugs With ETASU, Approved Indication, and Primary Goal

Brand Name	Generic Name	Primary Indication(s)	Key Goal(s) for REMS	Components of ETASU: Prescribers Have Certain Training or Special Certification	Dispensing Pharmacies and Other HCPs Have Special Certification	Drug Dispensed to Patients Only in Certain Health Care Settings	Drug Dispensed Only to Patients With Evidence of Safe-Use Conditions	Each Patient Using Drug Is Subject to Certain Monitoring	Each Patient Using the Drug Is Enrolled in a Registry	System to Monitor, Evaluate, and Improve Implementation of ETASU
Accutane (Amnesteem, Claravis, Sotret) capsules[a]	Isotretinoin	Severe nodular cystic acne	• Reduce the risk of fetal exposure	✓	✓		✓	✓	✓	
Actiq lozenge on a stick[a]	Fentanyl citrate	Breakthrough cancer pain	• Mitigate risk of overdose, abuse, addiction, and serious complication due to medication errors • Mitigate accidental exposure in children	✓	✓					
Aranesp injection	Darbepoetin alfa	Anemia	• Support informed decisions between patients and their HCPs by educating them on the risks of Aranesp • Mitigate risk of decreased survival and/or poorer tumor outcomes in patients with cancer	✓	✓		✓			✓
Clozaril tablets Fazaclo ODT[a]	Clozapine	Schizophrenia	• Avoid agranulocytosis	✓	✓		✓	✓	✓	
Entereg capsules	Alvimopan	Postoperative ileus	• Reduce the risk of myocardial infarction observed with longer use			✓	✓			✓
Epogen/Procrit injection	Epoetin alfa	Anemia	• Support informed decisions between patients and HCPs by educating them on risks • Mitigate risk of decreased survival and/or poorer tumor outcomes in patients with cancer	✓	✓		✓			✓
Exalgo extended-release tablets	Hydro-morphone hydrochloride	Management of moderate to severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time	• Inform patients and HCPs about the potential for abuse, misuse, overdose, and addiction • Inform patients and HCPs about safe use	✓						
Letairis tablets[b]	Ambrisentan	Pulmonary arterial hypertension	• Encourage informed benefit-risk decisions • Minimize the risk of hepatotoxicity • Minimize the risk of fetal exposure and adverse fetal outcomes in female patients of childbearing potential	✓	✓		✓			✓
Lotronex tablets[a]	Alosetron	IBS	• Ensure that patients and physicians are fully informed of the risks (ischemic colitis) and possible benefits • Ensure that only patients with severe, debilitating, diarrhea-predominant IBS, in whom benefits of the drug may exceed risks, are the target population • Ensure that only physicians with certain qualifications and who agree to accept certain responsibilities prescribe Lotronex	✓			✓			
Lumizyme	Alglucosidase alfa	Late-onset Pompe's disease	• Mitigate the potential risk of rapid disease progression in patients with infantile-onset Pompe's disease and with late (noninfantile) onset disease younger than 8 years • Ensure that the risks of anaphylaxis and severe allergic reactions are communicated to patients and prescribers • Ensure that the potential risks of severe cutaneous and systemic immune mediated reactions are communicated to patients and prescribers	✓	✓		✓			✓
Mifeprex tablets[a]	Mifepristone	Termination of intrauterine pregnancy	• Minimize bleeding and sepsis following medical abortion	✓	✓			✓		
Nplate for subcutaneous injection	Romiplostim	Thrombocytopenia	• Promote informed risk-benefit decisions before initiating treatment • Establish long-term safety and safe use through periodic monitoring of all patients for changes in bone marrow reticulin formation and bone marrow fibrosis, worsened thrombocytopenia after cessation of Nplate, thrombotic/thromboembolic complications, hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome, and medication errors associated with serious outcomes	✓	✓		✓	✓		✓
Onsolis buccal soluble film	Fentanyl	Breakthrough cancer pain	• Mitigate risk of overdose, abuse, addiction and serious complication due to medication errors • Mitigate accidental exposure in children	✓	✓		✓			✓
Oxycontin controlled-release tablets	Oxycodone hydrochloride	Pain	• Inform patients and HCPs about the potential for abuse, misuse, overdose, and addiction • Inform patients and HCPs about safe use	✓						
Promacta tablets	Eltrombopag	Thrombocytopenia	• Promote informed risk-benefit decisions before initiating treatment • Establish overall long-term safety and safe use through periodic monitoring of all patients for hepatotoxicity, bone marrow reticulin formation and risk for bone marrow fibrosis, worsened thrombocytopenia and increased hemorrhage risk after Promacta cessation, thrombotic/thromboembolic complications, and malignancies and progression of malignancy	✓	✓		✓	✓		✓
Revlimid capsules[a]	Lenalidomide	Myelodysplastic syndrome; multiple myeloma	• Prevent fetal exposure • Reduce the risk of fetal exposure from males taking Revlimid who engage in sexual contact with a female partner of child bearing potential • Educate physicians, other HCPs, and patients about potential lowering in blood cell counts (cytopenias)	✓	✓		✓	✓		
Sabril tablets and oral solution	Vigabatrin	Seizures; infantile spasms	• Reduce the risk of a Sabril-induced vision loss while delivering benefit to the appropriate patient populations • Inform patients/parent or legal guardian of the serious risks associated with Sabril, including vision loss and increased risk of suicidal thoughts and behavior	✓	✓		✓			✓
Soliris injection[b]	Eculizumab	Paroxysmal nocturnal hemoglobinuria	• Limit the occurrence and morbidity associated with meningococcal infections • Mitigate serious outcomes for patients who develop infection with Neisseria meningitidis and other systemic infections • Impart important safety information before initiating treatment by educating HCPs, patients, and caregivers on the important safety information associated with the use of Soliris, with an emphasis on meningococcal infection (Neisseria meningitidis), other serious infections, and possible serious hemolysis postdiscontinuation	✓					✓	✓
Sucraid oral solution	Sacrosidase	Sucrase deficiency	• Communicate the manufacturing change for Sucraid (sacrosidase) oral solution and ascertain whether there is any increase in allergy related adverse events for Sucraid oral solution following this change	✓			✓			✓
Thalomid capsules[a]	Thalidomide	Multiple myeloma; erythema nodosum leprosum	• No fetal exposure	✓	✓		✓	✓		✓
Tikosyn capsules[a]	Dofetilide	Atrial fibrillation/ flutter	• Minimize arrhythmia	✓	✓	✓		✓		
Tracleer tablets[b]	Bosentan	Pulmonary arterial hypertension	• Enable informed risk-benefit decisions for treating patients with Tracleer • Minimize the risk of hepatotoxicity in patients exposed to Tracleer • Minimize the risk of fetal exposures in female patients exposed to Tracleer • Educate prescribers, patients, and pharmacies on safe-use conditions for Tracleer	✓	✓		✓			✓
Tysabri injection[a]	Natalizumab	Crohn's disease; multiple sclerosis	• Minimize the risk of PML • Minimize death and disability due to PML • Promote informed risk-benefit decisions regarding Tysabri use	✓	✓	✓	✓	✓		✓
Xyrem oral solution[a]	Sodium oxybate	Excessive daytime sleepiness; cataplexy	• Mitigate risk of severe CNS events • Avoid abuse/diversion	✓						
Zyprexa Relprevv extended-release injection	Olanzapine	Schizophrenia	• Mitigate the risk of negative outcomes associated with Zyprexa Relprevv postinjection delirium/sedation syndrome	✓	✓		✓	✓	✓	✓

HCP = health care provider; IBS = irritable bowel syndrome; ODT = oral disintegrating tablet; PDSS = postinjection delirium/sedation syndrome; PML = progressive multifocal leukoencephalopathy.
[a] Deemed REMS.
[b] Originally deemed REMS; new approved REMS in 2009-2010.

CONCLUSIONS

- The majority (64%) of REMS require only a medication guide.
- ETASU are being used selectively, tailored to the specific product concerns.
- Provider certification and documentation of patient safe-use conditions are far more common than the other elements, including restricted product availability, patient monitoring, or patient registries.
- As noted in feedback to FDA Draft Guidance on REMS,[5,6] as use of ETASU increases, they may become more burdensome to health care prescribers and pharmacists.
- Shared learnings regarding design, implementation, and impact of REMS among stakeholders may help to minimize overall burden.

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