Evaluation of Current Risk Evaluation and Mitigation Strategies

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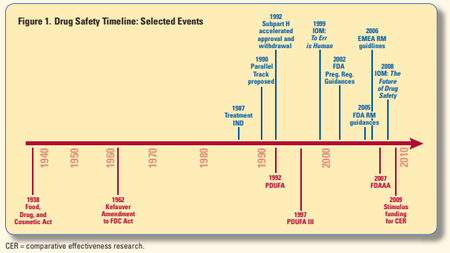
BACKGROUND

The role of the United States (US) Food and Drug Administration (FDA) with regard to postmarketing drug safety has increased over time (Figure 1).

Figure 1. Drug Safety Timeline: Selected Events



CER = comparative effectiveness research.

Under the 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 risk evaluation and mitigation strategies (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 to 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, which may include one or more of the following:
  - Health care providers who prescribe the drug have particular training or experience or are specially certified
  - 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:
  - Monitor and evaluate implementation of elements to assure safe use 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 by such persons.

OBJECTIVE

To review characteristics of active REMS in the US for drugs with significant known risks.

METHODS

For the ISPE abstract, we identified all drugs recognized by the FDA as having an active REMS as of October 31, 2008. To provide the most up-to-date information in this rapidly changing regulatory environment, REMS approved through July 31, 2009 are included in the results for the poster. This survey of programs updates a review previously published.[2]

Authors 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, elements to assure safe use; and whether the REMS was approved at the time of or following drug approval.

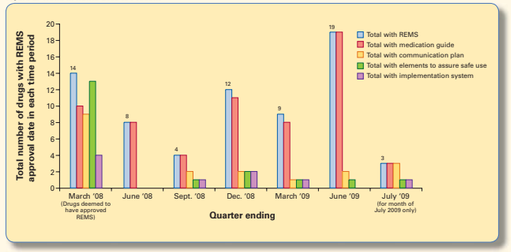
RESULTS

A total of 69 drugs were identified as having an approved REMS (14 "deemed" REMS as listed in the Federal Register[4] and 55 subsequently listed on the FDA website[3]).

Of the 69 REMS, 52% (n = 36) required only medication guides, 28% (n = 19) required communication plans, 28% (n = 19) required elements of safe use (13/19 are for drugs deemed to have approved REMS), and 13% (n = 9) required an implementation system.

The total number of REMS approved so far in 2009 (n = 31) accounts for 45% of all REMS approved. Figure 2 shows the trend in REMS components over time since March 2008.

Figure 2. Trend in REMS 2008 to Present



Figures 3 and 4 show the distribution of REMS by indication and the primary safety concern that prompted the REMS.

Figure 3. Distribution of REMS by Primary Indication Category

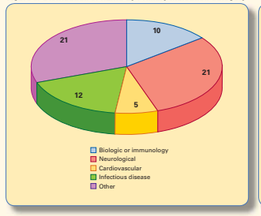
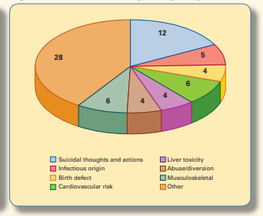


Figure 4. Distribution of REMS by Primary Safety Concern



All REMS aimed at preventing birth defects or abuse/diversion included elements to assure safe use. Table 1 shows drugs with approved REMS requiring a medication guide only.

Table 2 displays drugs with approved REMS requiring components beyond a medication guide.

Table 1. Approved REMS With Medication Guide as Only REMS

Drug (Generic)	Trade Name	Indication	Reason(s) for REMS
Abacavir sulfate, abacavir sulfate and lamivudine, abacavir sulfate, lamivudine, and zidovudine	Ziagen tablets and oral solution, Epzicom, Trizivir	HIV	Hypersensitivity reactions, especially if have HLA-B*5701 allele; increased risk MI
Budesonide and formoterol	Symbicort	Asthma	Death, anaphylaxis
Bupropion hydrobromide	Aplenzin extended-release tablets	Depression	Suicidal thoughts and behavior, seizures, hypertension
Ciprofloxacin	Cipro, Cipro XR, Proquin XR	Antibiotic	Tendinitis
Etanercept	Enbrel for subcutaneous injection	Arthritis, psoriasis, Crohn's disease, and ankylosing spondylitis	Histoplasmosis and other invasive fungal infections
Fenofibric acid delayed release	Trilipix	Reduce triglycerides	Rhabdomyolysis when used with a statin
Fluticasone propionate and salmeterol xinafoate inhalation powder	Advair Diskus/HFA	Maintenance treatment of asthma	Asthma-related death, infection, pneumonia
Gemifloxacin	Factive	Antibiotic	Tendinitis
Interferon alfa-2a	Intron A	Hairy cell leukemia, malignant melanoma, follicular lymphoma, AIDS-related Kaposi's sarcoma in chronic hepatitis B, chronic hepatitis C, and condylomata acuminata	Birth defects, suicidal or homicidal thoughts
Lacosamide	Vimpat injection	Seizures	Suicidal thoughts and actions
Lamotrigine	Lamictal	Epilepsy/seizures	Stevens-Johnson syndrome/suicidal thoughts and actions
Levetiracetam	Keppra, Keppra XR	Epilepsy/seizures	Suicidal thoughts and actions
Levofloxacin	Levaquin	Antibiotic	Tendinitis
Lopinavir and ritonavir	Kaletra	HIV	QT prolongation
Milnacipran hydrochloride	Savella	Fibromyalgia	Suicidal thoughts and actions
Moxifloxacin	Avelox	Antibiotic	Tendinitis
Nevirapine	Viramune tablets and oral suspension	Combination antiretroviral treatment of HIV-1 infection	Fatal and nonfatal hepatotoxicity and skin reactions
Norfloxacin	Noroxin	Antibiotic	Tendinitis
Olanzapine	Zyprexa, Zyprexa Zydis tablets	Antipsychotic	Hyperglycemia, hyperlipidemia, and weight gain
Olanzapine and fluoxetine	Symbyax capsules	Antidepressant	Hyperglycemia, hyperlipidemia, and weight gain; suicidal thoughts and actions
Pancrelipase	Creon	Pancreatic exocrine enzyme replacement	Fibrosing colonopathy
Peginterferon alfa-2a	Pegasys	Hepatitis C	Risks to pregnancy, mental health problems, blood problems, liver problems, infections, eye problems, and stroke
Pioglitazone and metformin	Actoplus met XR	Diabetes	Heart failure, angina/MI
Peginterferon alfa-2b, Redipen single-dose delivery system and Rebetol Ribavirin	PegIntron Rebetol Combo Pack	Hepatitis C	Life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. With ribavirin - birth defects
Pregabalin	Lyrica	Neuropathic pain, seizures, fibromyalgia	Suicidal thoughts and actions
Ramelteon	Rozerem	Insomnia	Worsening of depression, suicidal thoughts and actions
Rosiglitazone maleate and glimepiride	Avandaryl	Diabetes	Heart failure, angina/MI
Rosiglitazone maleate and metformin HCL	Avandamet	Diabetes	Heart failure, angina/MI/lactic acidosis
Rufinamide	Banzel	Seizures	Suicidal thoughts and actions
Sumatriptan succinate and naproxen sodium	Treximet tablets	Acute treatment of migraine attacks	Heart attack or stroke
Tapentadol	Nucynta	Moderate to severe acute pain	Respiratory depression, other severe side effects, diversion
Telbivudine	Tyzeka	Hepatitis B	Peripheral neuropathy
Topiramate	Topamax	Seizures and migraines	Suicidal thoughts and actions and serious eye problems
Venlafaxine hydrochloride extended release tablets	Venlafaxine hydrochloride	MDD and social anxiety disorder	Suicidal thoughts and actions
Zolpidem tartrate	Edluar, Zolpomist Spray	Insomnia	Abnormal "sleep" behavior/abnormal thoughts and behavior and memory loss
Zonisamide	Zonegran	Epilepsy/seizures	Metabolic acidosis

MDD = major depressive disorder; MI = myocardial infarction; XR = extended release.

Table 2. Drugs With Approved REMS With Additional Components

Drug (Generic)	Trade Name	Indication	Reason(s) for REMS	Medication Guide	Communication Plan	Elements to Assure Safe Use
Abarelix	Plenaxis	Prostate cancer	Allergic reactions	X	X	X
Abobotulinum-						
Alosetron	Lotronex	Irritable bowel syndrome	Ischemic colitis; complications of constipation	X	X	X
Alvimopan	Entereg capsules	Accelerate gastrointestinal recovery following surgery	MI in patients treated with opioids immediately prior to alvimopan use	No	X	X
Ambrisentan	Letairis	Pulmonary arterial hypertension	Liver injury, potential for fetal harm	X		X
Bosentan	Tracleer	Pulmonary arterial hypertension	Birth defects, liver toxicity	X		X
Certolizumab pegol	Cimzia	Crohn's disease	Infection	X	X	
Clozapine	Clozaril, Fazaclo	Schizophrenia	Agranulocytosis	No		X
Dofetilide	Tikosyn	Atrial fibrillation/flutter	Torsades de pointes	No		X
Eculizumab	Soliris	Paroxysmal nocturnal hemoglobinuria to reduce hemolysis	Meningococcal infections	X	X	
Eltrombopag	Promacta	Thrombocytopenia in patients with chronic immune ITP	Hepatoxicity, bone marrow reticulin formation and risk of bone marrow fibrosis	X		X
Fentanyl buccal soluble film	Onsolis	Break-through pain in adults with cancer	Abuse/diversion	X	X	X
Fentanyl citrate	Actiq	Cancer pain	Pediatric toxicity/abuse/diversion	X		X
Fentanyl PCA	Ionsys	Acute postoperative pain	Abuse/diversion	No		X
Golimumab	Simponi injection	Moderate to severe rheumatoid arthritis and ankylosing spondylitis	Histoplasmosis and other invasive fungal infections not consistently recognized	X	X	
Isotretinoin	Accutane, Amnesteem, Claravis, Sotret	Severe nodular cystic acne	Birth defects, depression, psychosis and, rarely, suicidal ideation	X	X	X
Lenalidomide	Revlimid	Myelodysplastic syndrome with deletion 5q cytogenetic abnormality	Blood clots, possibility of birth defects	X	X	X
Mifepristone	Mifeprex	Medical termination of pregnancy	Bleeding and sepsis following medical abortion	X	X	X
Natalizumab	Tysabri	Multiple sclerosis	Multifocal leukoencephalopathy	X	X	X
Prasugrel	Effient	Antithrombotic	Bleeding	X	X	
Romiplostim	Nplate for subcutaneous injection	Thrombocytopenia in patients with chronic immune ITP	Bone marrow reticulin formation and a risk for bone marrow fibrosis	X	X	X
Sacrosidase	Sucraid oral solution		Potential for allergic reaction following manufacturing change	No	X	X
Sodium oxybate	Xyrem	Cataplexy associated with narcolepsy	Severe CNS events/abuse/diversion	X	X	X
Telbivudine	Tyzeka	Hepatitis B	Peripheral neuropathy	X		
Teriparatide (rDNA origin) injection	Forteo	Osteoporosis	Osteosarcoma	X	X	
Tetrabenazine	Xenazine tablets	Chorea associated with Huntington's disease	Depression and suicidal thoughts and behavior	X	X	
Thalidomide	Thalomid	Cutaneous manifestations of erythema nodosum leprosum, multiple myeloma	Birth defects	No	X	X
toxinA injection	Dysport	Cervical dystonia and glabellar lines	Potential for medication error/distant spread of toxin beyond injection site	X	X	

CNS = central nervous system; ITP = idiopathic thrombocytopenic purpura; PCA = patient-controlled analgesia.

CONCLUSIONS

The requirement for medication guides and other REMS components is becoming relatively common following the FDA Amendments Act of 2007,[1] which authorized the FDA to require REMS. While existing REMS are highly targeted to specific events and often limited populations, some patterns are emerging. However, details of most existing programs are not readily available. The lack of publicly available information limits the knowledge base upon which new REMS are developed.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

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