Reducing Medication Use Risk: Managing High Alert Drugs and Implementing Federally Mandated Risk Evaluation and Mitigation Strategies (REMS)

Kenneth Dandurand, R.Ph., MS
Brenda Saxon, Pharm.D, MBA

April 2011

Clinical Pharmacy Associates
A Prescription for Accountable Healthcare

Introduction

Hospitals, Physicians, and Pharmacists continue to struggle with the management of high-alert drugs and the need to eliminate adverse drug events (ADE), thereby ensuring patient health and safety while controlling health costs. According to the Institute of Medicine (IOM), medication-related adverse events are a significant cause of medical error and account for a large portion of the mortality (up to 98,000 deaths annually) with increased hospital costs of up to $29 billion per year. [1] *Clear recommendations are provided to address REMS and help you meet regulatory quality compliance.*

Background

The FDA requires manufacturers to provide Risk Evaluation and Mitigation (REMS) to weigh the risks, but practitioners have specific responsibilities to provide patient advice.

Since the early 1960's, the Food and Drug Administration (FDA) has required drug manufacturers to disclose risks and adverse effects of approved medications. This includes recent requirements for black box warnings, patient package inserts, medications guides and post-marketing (phase IV) trials to reduce the risk associated with drug therapy. The recommendations made by the Committee on Quality of Health Care in America in its 2006 report "The Future of Drug Safety: Promoting and Protecting the Health of the Public"[2] outlined comprehensive approaches to improving patient safety, including how the FDA could improve its drug safety efforts, and was supported by the IOM. This was particularly important as FDA drug approval processes were streamlined to bring certain critical medications (e.g. antiretroviral) to market quicker and given the advent of gene-based therapies with high incidences of potentially life-threatening side effects. It became clear that among other recommendations, a formal communication method between the stakeholders (FDA, Manufacturers, Practitioners and Patients) is required to ensure patient understanding and consent. The Food and Drug Administration Amendments Act of 2007[3] gave the FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks. The result is that along with the requirements for product safety labeling changes and additional post-approval studies to assess serious drug risk, the FDA can now require Pharmaceutical companies to conduct Risk Evaluation and Mitigation Strategies (REMS). Prior to the new law, the FDA had limited recourse short of product removal to ensure risk management once a drug product was approved. The ultimate goal is to ensure that drug benefits outweigh their risks as is understood by everyone in the healthcare system.

REMS Strategies

On the surface these strategies appear to be focused on pharmaceutical companies however, healthcare organizations and professionals have a duty to assure communication and notice to patients. This could include development of medication guides, patient communication methods, tracking programs, documentation and implementation of elements to assure safe use. Combined with these risk mitigation strategies, other currently employed safety activities including adverse drug event monitoring, review of safety related changes in approved medications, and drug therapy formulary assessments are critical in developing strategies that will improve care, meet accrediting standards and reduce the expense of preventable medical error. This requires healthcare organizations to examine ways to meet the regulations by reviewing their current state in the management of high alert medications while supporting the implementation of processes which meet the FDA mandates for Risk Evaluation and Mitigation Strategy (REMS) that are compatible with a planned approach to overall institutional medication safety.

...patients with cancer need to be advised of these risks but Hospitals and Physicians must enroll and comply with the ESA APPRISE oncology program. The goal is to use these drugs when appropriate with an emphasis on limiting the exposure and the potential for side effects.

With drug companies increasing direct marketing to the public and consumers more often requesting these medications from their physicians there is enhanced potential for over prescribing. Unfortunately the public is less likely to appreciate or understand the cautions and potential side effects of these drugs. While practitioners report adverse events on a voluntary basis, only a small fraction of the total events are routinely reported. While these reports are essential to assuring quality medication use, the retrospective nature makes it imperative that the Food and Drug Administration prospectively develop guidelines in areas of known risk. The current list contains more than 100 drugs, with approximately 10% requiring detailed documentation that must be followed by prescribers and dispensers. For example, the REMS process for Erythropoietin Stimulating Agents (ESAs) indicates that the supply of drug can be denied if certain procedures are not in place and documented. This can also have a profound impact on reimbursement and patient care. ESAs have seen widespread use over the last decade to improve red blood cell production in immuno-suppressed, cancer and renal failure patients. In many cases these drugs are life saving. Unfortunately, in some post-marketing clinical studies it has been shown that ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in patients with breast, non-small cell lung, head and neck, lymphoid and cervical cancers. Not only must patients with cancer be advised of these risks but Hospitals and Physicians must enroll and comply with the ESA APPRISE oncology program. The goal is to use these drugs when appropriate with an emphasis on limiting the exposure

and the potential for side effects.

While many organizations have instituted a variety of procedures to address patient safety goals, they tend to lack a strategic and sustainable approach. In addition to a strategic approach, practitioners must review their activities when and wherever reports of potential fatal adverse events are reported to determine whether their procedures require modification. If a facility has no opportunity to accomplish this review in a timely manner, the institution can be at risk for repeating catastrophic events. An analysis and programmatic approach of this type can often require perspective and resources beyond the usual levels required to maintain day-to-day medication use functions. Diminishing resources, ever-changing technology, complex therapies, and newly marketed pharmaceutical products impact administrators and managers. The entire healthcare system is being challenged to implement high-leverage medication error prevention strategies to reduce the possibility of patient harm.

Time and resources must be set aside to routinely evaluate ongoing processes, respond to events, and develop changes, often multi-disciplinary, to continue to provide a safe environment at each facility.

Health care providers are having difficulty reducing risk as they manage their drug formularies. While there are many versions of compliance, many of the elements or the spirit of the regulation are not met. Time and resources must be set aside to routinely evaluate ongoing processes, respond to events, and develop changes, often multi-disciplinary, to continue to provide a safe environment at each facility. Ongoing access to FDA actions, risk literature, adverse medication events, **Highlights of Safety Related Drug Labeling Changes™**, legal citations, and **New Drug Classifications™** are essential to maintain patient safety.

Recommendations:

To address REMS, as well as meet state and regulatory quality compliance, the following steps provide a helpful outline:

- Include REMS in current risk assessment/reduction plan
- Assess new FDA approved medications for REMS and incorporate into formulary and adverse drug event process
- Monitor for REMS designation on drugs monthly
- Assign quantifiers to assess success of REMS implementation and compliance
- Incorporate REMS notification into order entry, verification and administration process

Below is a list of drugs identified by the FDA, which require REMS. REMS components vary by drug and health care organizations must determine methods to achieve compliance. The attached list represents only the drugs beginning with the letter “A”.4

Drugs Requiring REMS

Name	Application	Date REMS Approved	REMS Components (All REMS include timetable for assessment)
Actemra (tocilizumab) Injection (PDF - 456KB)[1]	NDA 22-024	1/8/2010	medication guide, communication plan
Actoplus Met (pioglitazone hydrochloride and metformin hydrochloride) Tablets (PDF - 13KB)[2]	NDA 21-073/S-037	9/14/2009; modified 10/21/2009	medication guide
Actoplus Met XR (pioglitazone and metformin) Extended-Release Tablets (PDF - 79KB)[3]	NDA 21-077/S-029	5/12/2009	medication guide
Actos (pioglitazone hydrochloride) Tablets (PDF - 61KB)[4]	NDA 21-254/S-007	9/9/2009	medication guide
Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) (PDF - 35KB)[5]	NDA 22-250	4/30/2008	medication guide
Advair HFA (fluticasone propionate and salmeterol xinafoate inhalation powder) (PDF - 12KB)[6]	NDA 21-015/S-022	7/31/2008; modified 9/15/2009	medication guide
Ampyra (dalfampridine) Extended-Release Tablets (PDF - 60KB)[7]	NDA 22-108	1/22/2010	medication guide, communication plan
Androgel (testosterone) Gel (PDF - 86KB)[8]	BLA 103951/5197	9/18/2009	medication guide
Aplenzin (buproprion hydrobromide) Extended-Release Tablets (PDF - 31KB)[9]	NDA 21-410/S-025	4/23/2008	medication guide
Aranesp (darbepoetin alfa) Injection (PDF - 11288KB)[10]	NDA 21-700/S-008	2/16/2010	medication guide, communication, elements to assure safe use, implementation system
Avandamet (rosiglitazone maleate and metformin[11] hydrochloride) Tablets (PDF - 96KB)[12]	NDA 21-085/S-042, 21-277/S-036	12/2/2008	medication guide
Avandaryl (rosiglitazone maleate and glimepiride) Tablets (PDF - 96 KB)[13]		12/2/2008	medication guide
Avelox (moxifloxacin) Tablets and I.V. Solution (PDF - 20KB)[14]		4/27/2009	medication guide

REFERENCES

1. Institute of Medicine: To Err is Human: Building a Safer Health System, March 1999.
2. Institute of Medicine: The Future of Drug Safety: Promoting and Protecting the Health of the Public, September 2007.
3. Food and Drug Administration Amendments Act (FDAAA), September 2007.
4. Food and Drug Administration: www.fda.gov/drugs/drugsafety/postmarketingdrugsafetyinformationforpatientsandproviders/ucm111350.htm