REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 3-I-12

Subject: Risk Evaluation and Mitigation Strategies

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Referred to: Reference Committee K
(Michael D. Chafty, MD, Chair)

INTRODUCTION

Policy D-100.971 directs the American Medical Association (AMA) to work with the pharmaceutical and biological industries to increase physician awareness of risk evaluation and mitigation strategies (REMS) as a means to improve patient safety. The Council previously addressed the issue of REMS in Council on Science and Public Health Report 8-A-10.[1] By providing an update of REMS programs in the U.S., this report can serve as a contemporary resource for helping to increase physician awareness of this issue.

METHODS

Information for this report was largely based on information gleaned from ongoing staff drug policy activities, the internet sites of the U.S. Food and Drug Administration, and the REMS tracker maintained by the law firm of Hyman, Phelps, and McNamara.

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 outweigh the risks of the drug, or it can be required post-approval if new safety information emerges that requires use of this approach to keep the drug on the market. Manufacturers are accountable for development of the REMS program, certification and education of physicians, collection of performance and outcomes data, as well as surveillance and assessment of program effectiveness. FDA authority to require a REMS was vested in the 2007 Food and Drug Administration Amendments Act (FDAAA).[2] A REMS can include: (1) medication guide or patient package insert; (2) communication plan for health care practitioners; and (3) elements to ensure safe use.[2] As designed, a REMS also includes an implementation system, a sponsor's plan to assess the performance of the REMS, and a timetable for assessment.

Medication guides may be required if FDA determines that patient awareness of serious risk(s) could affect their decision to use the product, information in the guide could help prevent serious adverse effects, or the drug product is important to patient health and patient adherence to directions for use are critical to the drug's effectiveness.[3] 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.[4]

Action of the AMA House of Delegates 2012 Interim Meeting: Council on Science and Public Health Report 3 Recommendations Adopted and Remainder of Report Filed.

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 present 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 begun moving toward a so-called "single document" solution for written patient information 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.

Originally, medication guides were an integral component of virtually all REMS programs. Between the time when the REMS provision of FDAAA took effect and January 1, 2011, FDA approved more than 150 medication guides as part of a REMS; more than 70% of these REMS were based on the medication guide only. Subsequently, the FDA issued Guidance[5] that outlined a procedure for sponsors to request removal of medication guides from REMS. Based on this procedure and decisions that some REMS are no longer required to ensure patient safety, more than 100 REMS have been "retired." In most cases moving forward, the FDA expects to include a medication guide as part of REMS only when the REMS includes elements to ensure safe use.

Elements to Ensure Safe Use (Restricted Distribution)

Currently, of greatest concern to physicians are those drugs with REMS that include so-called "elements to assure safe use"[2] (ETASU), also referred to as restricted distribution. Elements to ensure safe use include the following general categories.[2] 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 or the drug is available only from a single central pharmacy;
- 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; patient undergoes specific informed consent or is enrolled in specific program; drug dispensed by special courier; patient must already be opioid-tolerant);
- Each patient using the drug is subject to certain monitoring or required benefit-risk assessment; and
- Prescribers, pharmacies, and/or treated patients must be enrolled in a registry.

<u>Currently Approved REMS</u>

As of August 14, 2012, REMS were approved for 69 products as follows:[6,7]

- 19 REMS with medication guides only;
- 22 REMS included a communication plan only;
- 9 REMS included a medication guide and a communication plan;
- 26 individual REMS included ETASU (most of these also include a medication guide and communication plan).

In addition, three currently approved single shared system REMS exist: (1) isotretinoin (IPLEDGE; six different generic manufacturers); (2) transmucosal immediate-release fentanyl products (sublingual tablets and spray, transmucosal lozenge, buccal tablets and film, and nasal

spray formulations); and (3) long acting opioids (long-acting/extended release opioid drugs, oral methadone, and transdermal fentanyl products). A few drugs (clozapine, smallpox vaccine, sodium oxybate) still exist that were approved with restricted distribution programs prior to FDAAA and creation of the REMS framework. Such products are "deemed" to have a REMS but do not appear on the FDA's list of approved REMS.[8]

Working with Industry

The AMA has demonstrated its commitment to working with industry on the opioid REMS by providing public commentary, participating in stakeholder meetings of the industry working group, and expressing a willingness to participate in the voluntary education of physicians on the safe and effective use of long-acting opioid products.

COMMENT

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. Patient safety is of paramount importance to physicians; however, strategies to ensure the safe use of prescription drugs need to be evidence-based and administratively simple in order to succeed.

Of equal, and perhaps greater concern, is the trend for prescriber training becoming a key element of risk management for prescription drugs. Recently, the FDA approved the first drug for the prevention of sexually transmitted HIV infections (emtricitabine plus tenofovir, Truvada®) with a REMS program that includes prescriber training and education. This comes on the heels of the approval of a new weight loss drug (phentermine plus topiramate, Qsymia™) which requires prescriber training, as well as pharmacy certification. FDA's push to include more educational programs, including verification of completion of such training, could suggest an expanded role for continuing medical education (CME) as part of the REMS process. Such an approach is an integral element of the class-wide opioid REMS program, although the education in this instance is voluntary. Using industry-funded CME as a centerpiece of mandatory prescriber training within a REMS program raises an entire set of additional concerns related to manufacturer and stakeholder involvement in the design of such programs, enforcement, program integrity and administrative burdens.

Current AMA policy remains relevant in seeking to have the FDA establish a procedure for physician and other stakeholder involvement early in the REMS development process,

standardizing the REMS processes, creating REMS that are patient-centric, and establishing methods and metrics to assess the impact of ETASU on clinical practice and health outcomes.

RECOMMENDATION

The Council on Science and Public Health recommends that Policy H-100.961—The Evolving Culture of Drug Safety in the United States: Risk Evaluation and Mitigation Strategies (REMS) be amended by insertion and deletion to read as follows and the remainder of the report be filed.

(1) The Food and Drug Administration (FDA) issue a final industry guidance on Risk Evaluation and Mitigation Strategies (REMS) with provisions that: (a) urge~~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; and (c) recommend ~~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~~.

(2) The FDA, in concert with the pharmaceutical industry, evaluate the evidence for the overall effectiveness of REMS with ETASU in promoting the safe use of medications and appropriate prescribing behavior.

(~~2~~3) 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.

(~~3~~4) 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.

(~~4~~5) 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.

(6) The FDA solicit input from the physician community before establishing any REMS programs that require prescriber training in order to ensure that such training is necessary and meaningful, requirements are streamlined and administrative burdens are reduced. (Modify Current HOD Policy)

Fiscal Note: Less than $500

REFERENCES

1. Council on Science and Public Health Report 8. The evolving culture of drug safety in the United States: Risk evaluation and Mitigation Strategies (REMS). American Medical Association. Annual Meeting. June 2010. Chicago, IL

2. Food and Drug Administration Amendments Act (Public Law 110-85). Title IX, Section 505-: Risk Evaluation and Mitigation Strategies (REMS).

3. 21 CFR. Part 208. Medication Guides for Prescription Drug Products.

4. U.S. Department of Health and Human Services. Food and Drug Administration [Docket no. FDA-2009-N-0295]. Providing effective information to consumers about prescription drug risks and benefits; Public workshop. Fed Reg. 2009;74:33205-33207.

5. U.S. Food and Drug Administration. Guidance. Medication Guides─Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies. November 2011.

6. Approved Risk Evaluation and Mitigation Strategies. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm. Accessed August 14, 2012.

7. Hyman, Phelps, and McNamara. REMS Tracker. http://www.fdalawblog.net/fda_law_blog_hyman_phelps/files/REMS_Tracker.xls. Accessed August 14, 2012.

8. U.S. Department of Health and Human Services. Food and Drug Administration [Docket No. FDA–2008–N–0174]. Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007. http://www.fda.gov/OHRMS/DOCKETS/98fr/E8-6201.pdf. Accessed August 14, 2012.