Ensuring drug safety in health systems:
Role of the Food and Drug Administration
Amendments Act of 2007, risk evaluation
and mitigation strategies, and restricted drug
distribution systems
Ensuring drug safety in health systems: Role of the Food and Drug Administration Amendments Act of 2007, risk evaluation and mitigation strategies, and restricted drug distribution systems

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See page S21 or http://ce.ashp.org to locate the continuing-education learning objectives, self-assessment questions, and instructions covering the articles in this supplement.
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Introduction

Rita Shane


I

n the past, the Food and Drug Administration (FDA) was criticized for delays in the approval of potentially life-saving drugs; this criticism led to efforts to expedite the drug-approval process. However, the studies used to obtain product approval typically involve limited patient populations, and serious adverse events often do not become apparent until after approval. FDA has made an effort to develop more robust postmarketing surveillance processes to ensure drug safety. The FDA Center for Drug Evaluation and Research recently reorganized and expanded its Office of Surveillance and Epidemiology (formerly the Office of Drug Safety). Previously, this office operated separately from the FDA Office of New Drugs, but these two offices recently established a memorandum of agreement to collaborate in the management of significant safety issues involving pending and approved drug products.

The Food and Drug Administration Amendments Act (FDAAA) of 2007 enhanced the postmarketing authorities of FDA with respect to drug safety. This legislation has important implications for health-system pharmacists. The FDAAA grants FDA new authorities to require postmarketing studies or clinical trials of drugs and to require risk evaluation and mitigation strategies (REMS) for managing known or potential serious drug risks. Health-system pharmacists may find the requirements for REMS daunting. Patients may be deterred from using drug products with REMS requirements because of the safety information provided.

Restricted drug distribution systems established by specialty pharmacies, group purchasing organizations, wholesale distributors, or other specialty suppliers may be a component of REMS. These systems present challenges for health-system pharmacists, with important logistical, financial, and safety implications for patients and health systems. The specialty drug products supplied through specialty pharmacies and other restricted distribution systems are among the costliest available (e.g., injectable biotechnology products).

The first article in this supplement describes the drug safety provisions of FDAAA, including REMS, and the implications for health-system pharmacists. The second article discusses the impetus for these REMS and their evolution, their components, and their impact on patients, health
The Food and Drug Administration Amendments Act of 2007: Drug safety and health-system pharmacy implications

BRIAN M. MEYER

The Food and Drug Administration Amendments Act (FDAAA) of 2007 was signed into law on September 27 of that year. It amends the Federal Food, Drug, and Cosmetic Act, which provides the statutory authority for FDA. The need to reauthorize the Prescription Drug User Fee Act (PDUFA), which has a five-year sunset clause after which it ceases to be effective, served as the primary impetus for passage of the FDAAA. The FDAAA reauthorized the PDUFA, which was set to expire on September 30, 2007. Reauthorization of the PDUFA is required every five years; the legislation has been reauthorized three times since 1992, and reauthorization will be required again in 2012. The current PDUFA (known as PDUFA IV) authorizes FDA to collect user fees from manufacturers of human drug and biological products, which facilitates the FDA review process and expedites approval of these products.

References
FDAAA
The FDAAA is a lengthy document with 11 "titles" addressing various topics, including medical device user fees, the use of prescription drugs and medical devices in pediatric atric patients, and disclosure of and access to clinical trial databases. Title IX of the FDAAA enhances the postmarketing authorities of FDA with respect to drug safety, and section 901 of that title is particularly noteworthy because it grants FDA new authorities to require postmarketing studies or clinical trials of human drugs and to require risk evaluation and mitigation strategies (REMS). These new authorities were the result of experience with cyclooxigenase-2 inhibitors and certain other problematic drugs in the marketplace and a lack of clear authority for the agency to require that manufacturers conduct postmarketing research to clarify safety concerns surrounding such drugs. Recommendations from the Institute of Medicine for an enhanced role and authority of FDA in postmarketing information gathering on drug safety also contributed to the enactment of these provisions in the FDAAA.3

The FDAAA authorizes FDA to require postapproval studies or clinical trials of a drug product to assess a known serious risk related to use of the product, to assess signals of a serious risk related to use of the product, or to identify an unexpected serious risk when available data indicate the potential for a serious risk. 1 The FDAAA also allows FDA to require changes in the approved product labeling as indicated on the basis of new safety information generated after approval.

Risk minimization action plans, which are safety programs designed to minimize risk associated with a product, were required by FDA prior to enactment of the FDAAA.4 The REMS and postmarketing safety activities outlined in the FDAAA represent the evolution of FDA requirements for improving drug safety.

REMS
FDA may require a manufacturer to submit proposed REMS prior to approval and marketing of a drug product to ensure that the drug’s benefits outweigh its risks.1 Factors taken into consideration by FDA in determining whether REMS are required before product approval are listed in Table 1.

FDA may require postapproval REMS for drug products without REMS prior to approval if new safety information suggests that such strategies are needed to ensure that the drug’s benefits outweigh its risks.1 Possible sources of this new safety information include clinical trials (e.g., the postmarketing clinical trials required by FDA through the FDAAA), adverse event reports, the peer-reviewed biomedical literature, and FDAs new Sentinel Initiative, which is a national strategy for monitoring drug and medical product safety.1,3

The FDAAA requirements for REMS include assessments 18 months, three years, and seven years after the strategy is initially approved. However, the seven-year assessment may be omitted if FDA determines that any serious risks associated with the drug have been adequately identified and assessed and are adequately managed.9

Components of REMS may include a medication guide and package insert for distribution to patients.6 Possible additional components include a communication plan for health care providers (e.g., sending letters to health care providers, corresponding through professional organizations).

The FDAAA also has provisions to support safe access to drugs that have known serious risks and that would otherwise be unavailable.6 As part of REMS FDA may require the use of one or more of the elements listed in Table 2 to ensure safe use of such drugs because of their inherent toxicity or potential harmfulness.6 Restricted drug distribution systems provide some of these elements.

The FDAAA requires the FDA Drug Safety and Risk Management Advisory Committee to seek input from patients, physicians, pharmacists, and other health care providers about how the elements to ensure safe use may be standardized so as not to be unduly burdensome for the health care delivery system or to needlessly limit patient access to a drug. The FDAAA calls for a mechanism for evaluating at least annually the elements for one or more drugs.

FDA held a public meeting in late May 2009 to obtain input into the development of REMS for extended-release opioid analgesics.7 A notice of the meeting was published in the Federal Register, and testimony was received from more than 80 individuals and representatives of organizations, including the American Society of Health-System Pharmacists (ASHP), other pharmacy organizations, and patient advocacy groups. In its testimony, ASHP emphasized the need to standardize REMS and

Table 1.
Considerations in Determining the Need for Risk Evaluation and Mitigation Strategies before FDA Approval of a Drug Product

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated size of the population likely to use the drug</td>
<td>Seriousness of the disease or condition for which the drug will be used</td>
</tr>
<tr>
<td>Seriousness of the disease or condition for which the drug will be used</td>
<td>Expected benefit from the drug with respect to the disease or condition</td>
</tr>
<tr>
<td>Expected benefit from the drug with respect to the disease or condition</td>
<td>Expected or actual duration of treatment with the drug</td>
</tr>
<tr>
<td>Expected or actual duration of treatment with the drug</td>
<td>Seriousness of any known or potential adverse events related to use of the drug</td>
</tr>
<tr>
<td>Seriousness of any known or potential adverse events related to use of the drug</td>
<td>Background rate of such events in the population likely to use the drug</td>
</tr>
<tr>
<td>Whether the drug is a new molecular entity</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Elements to Ensure Safe Use of Drugs with Known Serious Risks as Part of FDA Risk Evaluation and Mitigation Strategies\(^{6,a}\)

<table>
<thead>
<tr>
<th>Element</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Special training, experience, or certification of health care providers</td>
<td>who prescribe the drug</td>
</tr>
<tr>
<td>Special certification of pharmacies, practitioners, or health care</td>
<td>settings that dispense the drug</td>
</tr>
<tr>
<td>Dispensing of the drug to patients only in certain health care settings</td>
<td>such as hospitals</td>
</tr>
<tr>
<td>Dispensing of the drug to patients with evidence or other documentation</td>
<td>of safe-use conditions, such as laboratory test results</td>
</tr>
<tr>
<td>Use of special monitoring for each patient receiving the drug</td>
<td></td>
</tr>
<tr>
<td>Enrollment of each patient receiving the drug</td>
<td></td>
</tr>
<tr>
<td>Enrollment of each patient receiving the drug in a registry</td>
<td></td>
</tr>
</tbody>
</table>

\(^{6,a}\)FDA may require one or more of these elements as part of risk evaluation and mitigation strategies to ensure the safe use of a drug because of its inherent toxicity or potential harmfulness.

...conduct research to determine which elements in Table 2 mitigate the risks associated with opioid analgesics. ASHP advocated exemption of hospital inpatients from REMS requirements because of the presence of safety systems in hospitals and health systems.

The fact that the extended-release opioid REMS will apply to a class of drugs rather than a specific agent has important implications. The FDAAA allows FDA to defer assessment of approved REMS for a drug class until one or more public meetings have taken place to consider possible responses. Public meetings may involve advisory committees, workshops, or both. Meetings are followed by publication of notices in the Federal Register and requests for comments. The process can be time consuming. The process for developing REMS for extended-release opioid analgesics has not yet concluded. The deadline for written comments was June 30, 2009.

**Conclusion**

The FDAAA arose from postmarketing drug safety concerns, and requirements for REMS represent the evolution of FDA drug safety requirements. The agency recognizes the need to balance the risks and benefits of drugs, the need for patient access to drugs with known serious risks, and the need to minimize the burden of requirements for REMS on health systems. Standardization of the elements to ensure the safe use of drugs with known serious risks is needed so that REMS are not unduly burdensome for the health care delivery system and do not needlessly limit patient access to the drugs.

**References**

Risk evaluation and mitigation strategies: Impact on patients, health care providers, and health systems

RITA SHANE

Purpose. To describe the impetus for and evolution, components, and potential impact on patients, health care providers, and health systems of risk evaluation and mitigation strategies (REMS) required by the Food and Drug Administration (FDA) for managing known or potential serious drug risks.

Summary. A 2006 report from the Institute of Medicine criticizing FDA for drug withdrawals due to safety problems provided the impetus for FDA to enhance postmarketing surveillance and to require REMS for medications with actual or potential safety concerns. Components of REMS may include medication guides, patient package inserts, communication plans for health care providers, and elements to ensure safe use (e.g., special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, use of patient registries). Recent increases in the number of drugs with REMS requirements, MedWatch alerts, and the development of the new Sentinel Initiative reflect FDA’s commitment to drug safety. Patients may be overwhelmed by information about drugs with REMS requirements, which could deter the use of potentially beneficial therapies. Pharmacists can help patients weigh the risks and benefits of drug therapy. Pharmacists, other health care providers, and health systems may find REMS requirements challenging, but FDA is cognizant of the need to balance the goals of ensuring drug safety and providing patient access to drugs without placing an undue burden on the health system.

Conclusion. The goal of improving drug safety is sought by the FDA, patients, health care providers, and health systems alike. Collaboration among health care providers may provide efficiencies in meeting FDA REMS requirements.

Index terms: Food and Drug Administration (U.S.); Patient information; Pharmacists; Postmarketing surveillance; Regulations; Risk management; Toxicity

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from stakeholders, including pharmacists, about mechanisms for minimizing the risks of medications with unusual safety and patient monitoring concerns. These mechanisms evolved into the current risk evaluation and mitigation strategies (REMS) required as part of the Food and Drug Administration Amendments Act (FDAAA) of 2007, which was signed into law in September of that year.

Efforts to minimize the risks associated with certain medications with known safety concerns began before the 2006 IOM report was released. For example, dispensing of the atypical antipsychotic agent clozapine has been contingent upon the results of baseline and periodic blood tests since the introduction of the drug in 1990, because of the risk of potentially life-threatening agranulocytosis.

Many RiskMAPs date back to October 2002, when the Prescription Drug User Fee Act III was enacted. By February 2007, a RiskMAP in some format (Table 1) had been established for 30 drugs. The simplest RiskMAPs involve education and outreach. Patient education with acknowledgment or use of an informed consent form was used in RiskMAPs for drugs such as thalidomide. Dispensing of a limited supply was used for drugs such as isotretinoin (30 days) and thalidomide (28 days).

Performance-linked access systems provide the greatest safeguards among the various formats for RiskMAPs. These systems limit access of target populations to drug products that have unique benefits but a high risk of irreversible morbidity or death. Such systems may require prescribing and dispensing only by specially trained and certified health care practitioners; dispensing only under conditions that meet evidence-of-safe-use requirements (e.g., negative pregnancy test results for thalidomide and isotretinoin); mandatory enrollment or registration of patients, prescribers, or pharmacists in restricted drug distribution programs or registries; and drug administration in special settings (e.g., inpatient hospitalization for at least three days during initiation of the antiarrhythmic agent dofetilide).

The biologic response modifier natalizumab, which is used for multiple sclerosis and Crohn’s disease, was temporarily withdrawn from the market in 2005 because of the risk of progressive multifocal leukoencephalopathy, an opportunistic infection of the brain that usually leads to death or severe disability. A restricted drug distribution program that requires drug administration by authorized infusion centers and registration of patients, prescribers, pharmacies, and infusion centers was implemented when the drug was reintroduced to the market in 2006. Prescribers and patients participating in this program are required to understand the risks associated with natalizumab treatment.

### Possible Formats for Risk Minimization Action Plans

<table>
<thead>
<tr>
<th>Format</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education and outreach: medication guides for patients, continuing-education programs for health care providers</td>
<td></td>
</tr>
<tr>
<td>Reminder systems: prompts, reminders, double checks, or guides for health care providers, patients, or both</td>
<td></td>
</tr>
<tr>
<td>Patient education with acknowledgment or use of informed consent forms</td>
<td></td>
</tr>
<tr>
<td>Health care provider attestation or acknowledgment</td>
<td></td>
</tr>
<tr>
<td>Dispensing of a limited supply</td>
<td></td>
</tr>
<tr>
<td>Performance-linked access systems</td>
<td>Prescribing and dispensing only by specially trained and certified health care practitioners</td>
</tr>
<tr>
<td></td>
<td>Dispensing only under conditions that meet evidence-of-safe-use requirements</td>
</tr>
<tr>
<td></td>
<td>Mandatory enrollment or registration of patients, prescribers, or pharmacists in restricted drug distribution programs or registries</td>
</tr>
<tr>
<td></td>
<td>Drug administration in special settings</td>
</tr>
</tbody>
</table>

*The strength of the safeguard increases from the top to the bottom of this list.*

Current FDA focus on safety

Evidence of a recent increase in emphasis on drug safety by FDA includes the addition of new REMS requirements for drugs, increased activity of the MedWatch program, an increase in the number of medications with black box warnings, and the Sentinel Initiative, a new national strategy for monitoring drug and medical product safety. MedWatch, FDA’s safety information and adverse event reporting program, provides information about safety alerts, recalls, market withdrawals, and key labeling changes. Currently, 430 drugs (including salt forms) are labeled with black box warnings. The goal of the Sentinel Initiative is active surveillance for safety problems instead of passive surveillance. Government and commercial databases (e.g., databases of managed care organizations and prescription benefit management companies) will be used in the Sentinel Initiative to conduct population surveillance and identify safety issues in groups of patients rather than relying on isolated case reports. A systematic approach using data from disparate data sources (Figure 1) will be used to monitor the effects of drugs in populations, identify safety problems and the need for drug-use modifications or restrictions, and facilitate an evidence-based approach to adverse drug event monitoring.
Drugs that are the subject of active safety alerts or recalls have increased markedly in recent months. In the course of only one week in early May 2009, four safety alerts were posted through the MedWatch program. These alerts involved (1) REMS under review for mycophenolate mofetil and mycophenolic acid to address the risk of pregnancy loss and congenital malformations, (2) the need for medication guides addressing the risk of suicide from antiepileptic drugs, (3) a new boxed warning on the labeling of testosterone gel cautioning against inadvertent secondary exposure of children to the gel, and (4) new safety information added to the labeling for erlotinib about gastrointestinal perforation; potentially fatal bullous, blistering, and exfoliative skin conditions; and corneal perforation and ulceration. Managing the alerts can be a challenge for pharmacists and other health care practitioners, who may be overwhelmed by the volume of alerts and may disregard important notices. At Cedars-Sinai Medical Center, information received through MedWatch about drug products known to be extensively used in the institution is communicated promptly to the medical staff through a newsletter and brought to the attention of the pharmacy and therapeutics committee and other medical staff committees as appropriate.

Increased postmarketing surveillance and frequent safety alerts also have the potential to affect patients by causing confusion and deterring the use of potentially beneficial drug therapies. Pharmacists can provide a valuable service to patients by helping them sort through the safety data to weigh the benefits and risks of drug therapy.

**Risk evaluation and mitigation strategies**

REMS are designed to manage a known or potential serious risk associated with a drug or biological product. The goal of REMS is similar to that of RiskMAPs, but REMS represent an increased focus on drug safety and postmarketing surveillance in response to criticism of FDA for failure to conduct such surveillance in the past. Drugs that were the focus of RiskMAPs were "grandfathered." The initial list of drugs "deemed to have in effect an approved REMS" in March 2008 (e.g., isotretinoin and clozapine, which were approved for marketing by FDA in 1982 and 1989, respectively) is shown in Table 2. As of July 2009, 52 drugs had approved REMS listed on the FDA website. Of these, ambrisentan is the only one that was on the initial list in March 2008.

Components of REMS may include medication guides, patient package inserts, or communication plans for health care providers (e.g., web-based educational materials, presentations to health care professionals by medical science liaisons) or elements to ensure safe use. Medication guides are handouts required by FDA for certain drug products that pose a serious and significant public health concern. The guides usually pertain to products used on an outpatient basis and are given to patients unless the physician determines that it is not in a particular patient’s best interest because of significant concerns about the effect of the medication guide on the patient. Medication guides are intended to provide information needed for

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**Table 2. Initial List of Drugs with Approved Risk Evaluation and Mitigation Strategies**

<table>
<thead>
<tr>
<th>Drug</th>
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<tbody>
<tr>
<td>Abarelix</td>
</tr>
<tr>
<td>Alosetron</td>
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<tr>
<td>Ambrisentan</td>
</tr>
<tr>
<td>Bosentan</td>
</tr>
<tr>
<td>Clozapine</td>
</tr>
<tr>
<td>Dofetilide</td>
</tr>
<tr>
<td>Eculizumab</td>
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<tr>
<td>Fentanyl PCA*</td>
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<tr>
<td>Isotretinoin</td>
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<tr>
<td>Lenalidomide</td>
</tr>
<tr>
<td>Mifepristone</td>
</tr>
<tr>
<td>Natalizumab</td>
</tr>
<tr>
<td>Smallpox (vaccinia)</td>
</tr>
<tr>
<td>Sodium oxybate</td>
</tr>
<tr>
<td>Thalidomide</td>
</tr>
</tbody>
</table>

*PCA = patient-controlled analgesia.
the safe and effective use of drug products. They tend to be lengthy, which can contribute to information overload for patients. Patients with literacy limitations or for whom English is not their primary language may have difficulty understanding medication guides. FDA has no requirements for creating medication guides in languages other than English, although translations are made by some institutions to accommodate their non-English-speaking patient populations.

The products chosen by FDA for medication guide development are those for which patient labeling could help prevent serious adverse effects, products with serious risks (relative to benefits) that patients should be made aware of because information about the risks could affect the decision to start or continue to use the product, or products that are important to health and for which patient adherence is crucial to effectiveness. Medication guides contain information approved by FDA and are part of the FDA-approved drug labeling. Currently, 240 drug products have medication guides. Medication guides may be required for drugs with or without REMS.

The need for REMS is determined by FDA at the time of drug approval, and REMS must be assessed at specified intervals. FDA also is required to conduct regular, biweekly screening of its Adverse Event Reporting System (AERS) database and post a quarterly report on the AERS website of any new safety information or potential signal of a serious risk identified by the AERS within the past quarter.

The FDAAA outlines elements to ensure safe use of drugs with known serious risks as part of REMS (e.g., special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, use of patient registries). The documentation required by FDA for meeting these requirements can be challenging for pharmacists and other health care practitioners. Elements to ensure safe use are currently required for only four drugs (alvimopan, romiplostim, eltrombopag, and sacrosidase).

Drugs with new REMS requirements anticipated in 2009 include botulinum toxin, because of problems related to spread of the drug from the area of injection to other areas of the body, and metoclopramide, because of tardive dyskinesia associated with chronic use. REMS for erythropoiesis-stimulating agents are also under consideration. Efalizumab, a psoriasis drug with REMS requirements, was voluntarily withdrawn from the market in 2009 because of progressive multifocal leukoencephalopathy.

The penalties that FDA may impose on manufacturers for violation of REMS requirements can be substantial, costing up to $250,000 per violation and $1 million for all violations adjudicated in a single proceeding. If a violation continues after the manufacturer receives written notice, a penalty of up to $10 million may be imposed for all violations in a single proceeding. In determining the amount of the penalty, FDA takes into consideration whether the company is making efforts to correct the violation.

Organizational approach to REMS requirements

At Cedars-Sinai Medical Center, the approach used to address the REMS requirements and elements to ensure safe use of new drugs is similar to what was previously established for natalizumab when the drug was reintroduced to the market, and for dofetilide. Initially, the pharmacy and therapeutics committee and medication safety committee were educated about the FDA requirements and elements to ensure safe use, but the need to extend these efforts to include the health-system administration, risk management nursing leadership, and medical staff was quickly recognized. The REMS requirements and elements to ensure safe use were integrated into the formulary evaluation process.

A task force was established at Cedars-Sinai Medical Center to develop an overall approach to evaluating new drugs with safety concerns. Roles and responsibilities of various members of the health care team for educating patients and other health care providers about safety concerns and collecting safety data about the new drug to meet REMS requirements were identified. Resources, including medication information, procedures to follow when a new order is received, and record-keeping requirements for each medication, are provided on the hospital’s intranet. For some medications, order sets are also created to ensure that REMS requirements for elements to ensure safe use are fulfilled. This approach was used initially for natalizumab.

In order to comply with the REMS requirements for romiplostim, which include elements to ensure safe use, the pharmacy and nursing management are responsible for ensuring the training of their respective staffs in safe use of the drug, orders for the drug are approved by the pharmacy director or a drug-use policy pharmacist, orders are filled after verification of patient and physician enrollment in the manufacturer’s REMS program, and patients receive the medication guide before starting treatment and again with each dose. The prescriber responsible for enrollment of inpatients must ensure that the drug will be available as needed from an outpatient provider who is also enrolled in the manufacturer’s REMS program. This responsibility is often shared with the pharmacy department to ensure continuity of drug therapy provided in the inpatient and outpatient settings. Other requirements of the program include maintenance of records by the pharmacy, performance of
complete blood counts and platelet counts weekly until values are stable and monthly thereafter, prompt reporting of adverse drug events, and completion of a safety survey every six months. There are a number of pharmacy record-keeping requirements as well.29

Opioid analgesics

Concerns about misuse, abuse, and accidental overdosage of extended-release opioid analgesics have led FDA to consider requiring REMS for this class of drugs.30 A public meeting was held in late May 2009, and written comments were solicited from stakeholders with a deadline for submission of June 30, 2009. A final rule is yet to be published. The REMS will apply to 24 products containing fentanyl, hydromorphone, oxycodone, oxymorphone, methadone, or morphine. Elements to ensure safe use are likely to be included. The large number of drug products and patients affected, need for extensive record keeping across the continuum of care, and potential for delays in providing patient care are concerns associated with REMS for these products. In a notice published by FDA in the Federal Register in April 2009 announcing the public meeting and soliciting written comments, the agency raised questions and sought input about the type of education and means for certifying prescribers to ensure that they understand the risks of extended-release opioid products, the proper selection of patients, and the importance of patient counseling about safe and proper use of the products.30 Education and certification of pharmacists and other health care providers who dispense or administer these products is another issue under evaluation by FDA. These providers may be asked to verify that the prescriber is properly certified. The type of education for patients and the need for a signed prescriber–patient agreement acknowledging the patient’s receipt of information about the risks and proper use of the medication are other factors under consideration by FDA in making its final rule. The prescriber–patient agreement could be required at the time of initiation of drug therapy and periodically thereafter.

FDA also sought input about whether and how controls might be established for distributors that provide extended-release opioid analgesics to pharmacies and other health care providers.30 The need to maintain an efficient drug distribution process without placing an undue burden on the health care system was acknowledged by FDA in its notice.

Nonprescription analgesics

In late April 2009, FDA issued a final rule requiring new organ-specific warnings and related labeling for nonprescription analgesic, antipyretic, and antirheumatic drugs.31 The warnings relate to severe liver toxicity from acetaminophen and stomach bleeding from nonsteroidal anti-inflammatory drugs (NSAIDs). The final rule takes effect on April 29, 2010, and applies to combination products containing acetaminophen or NSAIDs, as well as products containing these drugs as a single ingredient. Although aspirin has been the focus of much FDA concern, the new labeling requirements apply to all NSAIDs (e.g., ibuprofen, ketoprofen, naproxen).

Warnings will be required on the labels of products containing acetaminophen or NSAIDs advising patients who consume three or more alcoholic drinks a day to consult a doctor before taking the drug or other pain relievers/fever reducers.31 These warnings must appear in conjunction with warnings about liver damage from acetaminophen and stomach bleeding from NSAIDs.

A new warning will be required advising patients receiving warfarin to ask their doctor before taking acetaminophen, because acetaminophen can increase the anticoagulant effect of warfarin.31 Warnings will be strengthened in the acetaminophen labeling cautioning patients to avoid exceeding the maximum recommended dose and to avoid concomitant use with other products containing acetaminophen. The labeling of some manufacturers’ products already complies with the new FDA labeling requirements.

FDA was required to estimate the potential benefits of the nonprescription analgesic labeling changes.31 An annual cost savings of $5.6 to $16.8 million (in 2001 dollars) was projected; this was based on an estimated 1% to 3% annual reduction in adverse health events (e.g., poisoning, acute kidney failure). The savings projection is derived from reductions in hospitalizations, emergency department visits, use of dialysis, and deaths due to unintentional overdoses, using a value of $5 million for premature loss of a statistical life.

Some patient advocates concerned about the safety of nonprescription analgesics have speculated about the potential benefits of reclassifying these drugs to “behind-the-counter” status, similar to the approach currently used for pseudoephedrine, although the burden on pharmacists would be a consideration. ASHP supports the establishment of an intermediate category of drug products that would not require a prescription but would be available from a pharmacist after appropriate patient assessment and professional consultation.32 This intermediate class has been contemplated for certain drugs currently available only by prescription that could be used safely with appropriate pharmacist oversight. This oversight might improve the safe use of acetaminophen and NSAIDs without compromising patient access to or benefit from the drugs.

Patient perspective

Patients receive information about medications from a wide variety of...
sources, including health care professionals, direct-to-consumer advertisements, medication guides, patient package inserts, product websites, and other sources of drug-related information on the Internet. The messages from these sources may be complex and inconsistent, causing confusion. Thus, safety information could needlessly deter the use of potentially beneficial drug therapies.

Drugs for which REMS are established may present unique challenges for patients because of the potentially overwhelming information they are required to receive. A coordinated effort by pharmacists and other health care professionals is needed to communicate effectively with patients about drugs with REMS requirements.

**Health-system perspective**

The potential burden on pharmacists and health systems of FDA drug safety requirements is considerable, especially if, for example, REMS requirements were imposed for each of the 430 drugs and drug salts with black box requirements. FDA is cognizant of the need to balance the often competing goals of ensuring drug safety and providing patient access to potentially harmful drugs without imposing an undue burden on the health system. Restricted drug distribution programs often increase the complexity of the drug procurement process, cause delays in treatment, and create paperwork and logistical burdens for health care providers. To minimize this burden, ASHP advocates a standardized approach to REMS as part of established drug procurement systems.

Pharmacists and other health care providers have an opportunity to devise a one-stop-shopping approach for drugs with REMS requirements by creating a standard framework and sharing it with their colleagues. This approach could address patient selection based on established safety criteria, patient education, and required record keeping. Although the safety criteria might vary depending on the drug, a standard framework would be helpful. A database might be created and posted on the Internet to facilitate sharing of REMS information among institutions. Collaborative efforts could help reduce the workload involved in meeting REMS requirements both for health systems and for the pharmaceutical industry. Collaboration also could enable the compilation of safety data for population analyses in order to determine the presence and prevalence of adverse events associated with specific medications.

The role of group purchasing organizations, wholesalers, and specialty pharmacies in REMS standardization remains to be clarified. Currently, specialty pharmacies manage many drugs with REMS requirements. Pharmacists have a responsibility to educate members of the pharmacy and therapeutics, medication safety, and other medication-related committees and the pharmacy, medical, and nursing staffs about FDA REMS requirements. A centralized pharmacy resource (i.e., staff and infrastructure) should be established to coordinate REMS. This resource might be modeled after the investigational drug services provided by pharmacy departments, since many of the requirements are similar. Risk management personnel should be involved in evaluation of REMS as part of the formulary evaluation process.

The optimal approach to meeting FDA requirements for REMS remains to be determined. Establishing a dialogue among stakeholders throughout the supply chain (from manufacturer to provider) is the first step in creating partnerships to minimize the burden of these requirements. Patients should also be included in these partnerships to ensure that their perspectives are taken into consideration.

**Conclusion**

Recent increases in FDA drug safety activities reflect a greater commitment of the agency to postmarketing surveillance of drug safety than in the past. Efforts have been made by FDA to balance the need for improved drug safety with the need to provide patient access to drug products and avoid placing an undue burden on the health system. Collaboration among pharmacists and other health care providers is needed to minimize the burden of FDA drug safety requirements while improving patient safety.

**References**

11. U.S. Food and Drug Administration. The Sentinel Initiative: a national strategy for monitoring medical product...
SYMPOSIUM  Risk evaluation and mitigation strategies


SYMPOSIUM  Financial and safety considerations

Specialty pharmacies and other restricted drug distribution systems: Financial and safety considerations for patients and health-system pharmacists

BONNIE E. KIRSCHENBAUM

Purpose. To discuss the role of restricted drug distribution systems in the implementation of risk evaluation and mitigation strategies (REMS), health-system pharmacists’ concerns associated with the use of specialty pharmacies and other restricted drug distribution systems, reimbursement policies for high-cost specialty drugs, supply chain models for traditional and specialty drugs, and emerging trends in the management of and reimbursement for specialty pharmaceuticals.

Summary. Restricted drug distribution systems established by pharmaceutical manufacturers, specialty pharmacies, or other specialty suppliers may be a component of REMS, which are required by the Food and Drug Administration for the management of known or potential serious risks from certain drugs. Concerns of health-system pharmacists using specialty suppliers include access to pharmaceuticals, operational challenges, product integrity, financial implications, continuity of care, and patient safety. An ambulatory care patient taking a specialty drug product from home to a hospital outpatient clinic or inpatient setting for administration, a practice known as “brown bagging,” raises concerns about product integrity and institutional liability. An institution’s finances, tolerance for liability, and ability to skillfully manage the processes involved often determine its choice between an approach that prohibits brown bagging but is costly and one that permits the practice under certain conditions and is less costly. The recent shift from a traditional supply chain model to a specialty pharmacy supply chain model for high-cost pharmaceuticals has the potential to increase pharmaceutical costs for health systems. A dialogue is needed between health-system pharmacists and group purchasing organizations to address the latter’s role in mitigating the financial implications of this change and to help clarify the safety issues. Some health plans have shifted part of the cost of expensive drugs to patients by establishing a fourth tier of drugs with a large copayment based on a substantial percentage of the cost of the drug. The number and cost of specialty drugs are expected to increase in the future. New approaches and reimbursement models are emerging to manage the high cost of new pharmaceuticals.

Conclusion. Health-system pharmacists can improve drug safety and manage costs by collaborating with group purchasing organizations, establishing policies for brown bagging, and making efforts to reconcile drug therapy provided in different settings through traditional drug channels and specialty pharmacies or other restricted drug distribution systems.

Index terms: Costs; Drug distribution systems; Economics; Food and Drug Administration (U.S.); Health-benefit programs; Pharmacists, hospital; Pharmacy; Pharmacy, institutional, hospital; Regulations; Reimbursement; Risk management; Specialties; Toxicity

The Food and Drug Administration (FDA) requires risk evaluation and mitigation strategies (REMS) for managing known or potential serious risks from certain drugs. These REMS are approaches established by FDA for working with pharmaceutical manufacturers to reduce risk from the use of a particular product. Although REMS vary based on the drug product, they have a common framework and components.
The number of drugs with REMS requirements is increasing, reflecting an increasing commitment of FDA to postmarketing surveillance. Restricted drug distribution systems may be a component of REMS, although REMS requirements do not necessarily include restricted drug distribution systems. The scope of restricted drug distribution systems extends beyond fulfillment of REMS requirements. Restricted drug distribution systems are entrepreneurial or business approaches to working with manufacturers, third-party payers, or pharmaceutical distributors. Restricted drug distribution systems may be established by the manufacturer, specialty pharmacies, wholesale distributors, or other specialty suppliers, including businesses seeking to provide services related to the distribution and administration of drugs with known serious risks that would otherwise be unavailable or those that are not commercially available and require sterile compounding. Restricted drug distribution systems provide an avenue for manufacturers to implement REMS for medications that require escalation systems to ensure safe use.

Issues and concerns

In 2008, a task force was convened by the American Society of Health-System Pharmacists (ASHP) to identify key issues associated with specialty drug delivery to patients through restricted drug distribution systems (Table 1). The task force also identified “domains of concern” reflecting problems faced by patients, health care providers, and health facilities interacting with specialty pharmacies or other restricted drug distribution systems (Table 2). Concerns about access to the drug product arise for both the patient and the pharmacy that needs to supply the drug to the patient. A major consideration for members of the task force is the labor involved in understanding and implementing the individual requirements of each specialty pharmacy and the investment of time by purchasing, pharmacy, and nursing staff. Educating nurses and other health care providers about requirements for obtaining and handling the drug also is a concern. Products that are administered by portable or implantable infusion devices pose further concerns and educational needs. Many problems related to patient access can be traced to a lack of sufficient education and knowledge about the operations of specialty pharmacies or other restricted drug distribution systems and about the use of portable or implantable infusion devices.

Most products supplied through specialty pharmacies and other restricted drug distribution systems initially are used in ambulatory care. Rules and regulations relating to product integrity come into play when a patient initiates drug therapy on an outpatient or ambulatory care basis and then requires hospitalization and continuation of drug therapy either in the inpatient setting or in an outpatient clinic using a drug product obtained outside the institution (a practice known as “brown bagging”). Table 3 summarizes problems that may arise. Continuity of care is a consideration in providing drug therapy when patients make the transition from one setting to another. Fragmentation of care provided in multiple settings can lead to errors and compromise patient outcomes.

Drug products supplied through specialty pharmacies and other restricted distribution systems are among the costliest available, with a large impact on the pharmacy budget. The task force considered the financial impact of specialty pharmacies and the need to ensure patient safety to be vital issues. Relationships among health care providers in different practice settings and the use of evidence-based practice also were concerns for members of the task force. A report from the task force,

<table>
<thead>
<tr>
<th>Table 1. Considerations for Pharmacists Arranging Specialty Drug Delivery to Patients Through Restricted Drug Distribution Systems*</th>
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<tbody>
<tr>
<td>Evaluate health care market trends and evolving business models for managing chronic diseases</td>
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<tr>
<td>Consider size and complexity of hospitals and health systems and identify how patient medication needs are addressed in various settings (e.g., inpatient, outpatient, community, home care, long-term care)</td>
</tr>
<tr>
<td>Identify evolving issues regarding continuity of care that result from increased use of these models and the devices used to administer many of these medications</td>
</tr>
<tr>
<td>Identify challenges with policies and procedures, education, and communication and their impact on patient care and safety</td>
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*As identified by the ASHP Task Force on Caring for Patients Served by Specialty Suppliers.

<table>
<thead>
<tr>
<th>Table 2. Concerns of Patients, Health Care Providers, and Health Facilities Interacting with Specialty Pharmacies or Other Restricted Drug Distribution Systems*</th>
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<tbody>
<tr>
<td>Access considerations</td>
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<td>Time management</td>
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<tr>
<td>Education</td>
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<tr>
<td>Rules and regulations relating to product integrity</td>
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<tr>
<td>Continuity of care</td>
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<tr>
<td>Financial impact</td>
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<tr>
<td>Patient safety</td>
</tr>
<tr>
<td>Health care provider relationships</td>
</tr>
<tr>
<td>and evidence-based practice</td>
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</table>

*As identified by the ASHP Task Force on Caring for Patients Served by Specialty Suppliers.
with recommended approaches for addressing these concerns and solving problems, will be published in the American Journal of Health-System Pharmacy.

Organizational issues

A culture of safety is essential for supporting the smooth integration of REMS into a health system. Fulfilling REMS requirements will present a challenge if administrators merely pay lip service to the need to ensure safety.

The ASHP Section of Pharmacy Informatics and Technology recently conducted a survey of the use of informatics and technology for various purposes in health systems, including fulfillment of REMS requirements. The survey was designed to ascertain the extent to which the pharmacy or hospital information system is being used to simplify the handling of products with REMS requirements. Ideally, the information system allows the tracking of patients receiving drugs with REMS requirements and supplies of these drugs and provides information about REMS requirements and policies for fulfilling them by including these data in the drug master profile for each product with REMS requirements. The survey results suggest that more widespread use of informatics and technology to fulfill REMS requirements could help simplify the complex process involved. For example, incorporation of REMS requirements into the drug databases commonly used in pharmacy information systems (e.g., First DataBank, Medi-Span), with links to pharmaceutical manufacturer websites for reporting drug safety information, would facilitate greater use of informatics and technology in fulfilling REMS requirements.

Specialty pharmacies and suppliers

Health-system pharmacists often need to establish a working relationship with a specialty pharmacy or specialty distributor (e.g., wholesaler) to gain access to certain drug products with unique acquisition requirements and purchasing arrangements. These drug products are distributed through specialized channels outside traditional drug distribution mechanisms and include drugs with REMS requirements, drug products carved out from traditional distribution channels by manufacturers or wholesalers for various reasons, and fourth-tier drugs carved out by an insurer or payer with specific acquisition requirements for the patient to obtain coverage. The use of drug products provided by specialty pharmacies affects many aspects of patient care and presents logistical and financial challenges to the health care facility. Specialty pharmacies are usually under contract with third-party payers to provide a limited number of high-cost pharmaceutical products (e.g., injectable biological therapies, oral chemotherapy agents).7 Health-system pharmacists often struggle with issues related to patient safety, institutional liability, and reimbursement for these products. Specialty pharmacy has been characterized in a variety of ways. According to one description, specialty pharmacy involves the handling of biotechnology- or gene-based drug therapies that have one or more of the characteristics listed in Table 4.8 Several drug products supplied by specialty pharmacies are self-administered at home by infusion using implantable or external pumps after extensive patient education about the proper use of both the medication and the infusion device.

Specialty pharmacies are highly effective in marketing their services to payers. They claim to have greater knowledge of new clinical developments involving biotechnology and injectable products that affect payers’ approaches to coverage and reimbursement than do health-system practitioners or ambulatory care pharmacies that oversee traditional drug distribution systems. Specialty pharmacies also claim to have greater expertise in managing certain products, disease states, and patient populations through utilization management protocols for injectable products than do practitioners in traditional drug distribution systems. These utilization management
protocols ensure patients’ adherence to therapy in the home care setting. The protocols could be expanded to address REMS requirements for collection of safety data. Specialty pharmacies typically handle drug products with short shelf lives and special storage requirements (usually refrigeration). Specialty pharmacies also claim to have a better understanding of Centers for Medicare & Medicaid Services (CMS) reimbursement policies and rates and how the policies and rates influence commercial payers than do pharmacists who manage traditional drug distribution systems. Simplified and standardized billing, coordinated networks for home drug delivery and infusion services, and complete data capture capabilities that facilitate comprehensive outcomes reporting and analysis (an attractive feature that helps fulfill REMS requirements) are among the possible services offered by specialty pharmacies.

As the number of drug products with REMS requirements has increased, wholesale distributors working with pharmaceutical manufacturers have reorganized and positioned themselves to function as specialty suppliers for these products outside traditional distribution channels. Multiple new creative distribution channels for costly drug products have been established, and health-system pharmacists need to carefully consider and integrate these channels and carved-out products into their overall purchasing practices and strategies.

Group purchasing organizations can play a major role in coordinating specialty pharmacy and traditional drug purchasing contracts and distribution channels. Purchasing a biotechnology product through a specialty pharmacy on a cost-plus-markup basis is substantially more expensive than purchasing the product from a traditional wholesaler at a discounted contract price (i.e., cost-minus basis), and this difference has important financial implications for health systems that should not be ignored. Carving out the priciest drug products from the drug spending pool at the wholesaler level has a negative impact on the contract rates offered and prepayment status for health systems.

Access to specialty pharmaceuticals and specialty distributors can be complex and time consuming for patients, health-system pharmacists, and other professionals in health systems. Patient safety, drug cost, drug product integrity, and continuity of care must be taken into consideration in a challenging environment characterized by conflict related to regulatory requirements, the high cost of pharmaceuticals, and the financial interests of third-party payers.

Not all drugs with REMS requirements need to be obtained through specialty pharmacies or restricted drug distribution systems, and not all drugs handled by these entities have REMS requirements. For example, natalizumab is available through a restricted drug distribution program that requires drug administration by authorized infusion centers, but it does not have REMS requirements. Clozapine has REMS requirements, but it is not supplied by specialty pharmacies. Infliximab, a drug administered by intravenous (i.v.) infusion and associated with serious infectious complications (including fatalities), is available through specialty pharmacies, but it has neither a restricted drug distribution system nor REMS requirements. Epoprostenol, a drug without REMS requirements, is handled only by certain distributors and administered i.v. for the treatment of pulmonary hypertension. FDA required drug safety labeling changes for epoprostenol in 2008 because of an increased risk for hemorrhagic complications due to the drug’s potent inhibition of platelet aggregation. Understandably, the average health-system practitioner can be confused when it comes to knowing which rules and systems apply to which products.

**Pharmaceutical reimbursement**

The Medicare program as administered by CMS has three parts (A, B, and D). Part A includes hospital inpatient and outpatient services, nursing home care, home health care, and hospice care. Reimbursement for covered medications, including some oral cancer chemotherapies, administered pursuant to a physician’s care plan, falls into Part B, as do physician services, medical supplies (e.g., durable medical equipment), and end-stage renal disease services (Table 5). Hospital outpatient services are administered through Part A and the Outpatient Prospective Payment System (OPPS). The Medicare prescription drug program falls into Part D and covers outpatient prescription drugs. Reimbursable specialty drugs and biological products falling under Part A.
Table 5. Drug Products Covered under Medicare Part B

<table>
<thead>
<tr>
<th>Class of Drugs</th>
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<tbody>
<tr>
<td>Injectables furnished incidental to a physician’s service and usually not self-administered</td>
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<tr>
<td>Drugs administered via nebulizer or pump furnished by Medicare</td>
</tr>
<tr>
<td>Immunosuppressive drugs for organ transplantation</td>
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<tr>
<td>Hemophilia blood-clotting factors</td>
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<tr>
<td>Certain oral anticancer treatments</td>
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<tr>
<td>Oral antiemetics</td>
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<tr>
<td>Pneumococcal, influenza, and hepatitis B vaccines</td>
</tr>
<tr>
<td>Erythropoietin-like drugs for trained home dialysis patients</td>
</tr>
<tr>
<td>Iron dextran, vitamin D injections, and erythropoietin-like drugs administered by facilities specializing in the care of patients with end-stage renal disease</td>
</tr>
<tr>
<td>Osteoporosis drugs</td>
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</tbody>
</table>

B are reimbursed by CMS through OPPS in one of four ways. In 2009, the basis for reimbursement for new drugs for which a Healthcare Common Procedure Coding System code has not yet been assigned is 95% of the average wholesale price. If daily costs exceed the threshold of $60, the costs for “packaged products” usually are purchased at a contract price (i.e., drugs prescribed and dispensed for self-administration by the patient). They also include biological products, insulin, medical supplies associated with the injection of insulin (e.g., syringes, needles, alcohol swabs, sterile gauze), and certain vaccines not covered under Part A or B. Pneumococcal and influenza vaccines are covered by Part B. Hepatitis B vaccine is covered under Part B for individuals at high or intermediate risk; for all other individuals, it could be covered under Part D. All other currently available vaccines and future vaccines would be covered under Part D, but coverage could be subject to plan prior-authorization requirements for demonstrating medical necessity.

A new fourth tier of drugs has been added to prescription drug plans by some third-party payers and insurers in response to pressure from employers to reduce health care costs. Patients participating in these plans are required to pay 20–30% of the cost of certain high-cost drug therapies used to treat certain illnesses (e.g., cancer, rheumatoid arthritis, multiple sclerosis) instead of the flat copayments required for most drugs. This approach shifts some of the cost of the most expensive drugs to patients. Some of these drug therapies cost as much as $15,000 per month, and the out-of-pocket cost of copayments for patients is substantial, although many plans have a cap (i.e., maximum).

Supply chain models

In recent years, the approach used for supply of certain high-cost pharmaceutical products has shifted from a traditional model to a specialty pharmacy model. The patient’s source of prescription drug products and the roles of the hospital or health-system pharmacy and group purchasing organizations differ between a traditional and a specialty pharmacy supply chain model (Table 6). In a traditional model, patients obtain prescription drugs from an outpatient, retail, or mail order pharmacy. Hospital and other health-system pharmacies purchase drug products usually at a contract price from a traditional wholesaler on a volume, cost-minus basis. The group purchasing organization negotiates contract pricing for products and wholesaler agreements, and rebates usually apply.

By contrast, in the specialty pharmacy model, patients obtain prescription drugs from mail order or specialty pharmacies, with the payer often dictating a single source for each product. Drugs with REMS requirements are supplied by specialty pharmacies. Compounded drugs may be obtained from specialty pharmacies or a physician (e.g., an anesthesiologist who supplies opioid analgesics for epidural administration using an implantable pump). If a hospital or health-system pharmacy is involved in providing drug therapy to the patient, drug products usually are purchased from specialty suppliers on a cost-plus-markup basis without the benefit of contract prices, volume discounts, or rebates.

The shift from a traditional to a specialty pharmacy supply chain model has the potential to increase costs for health systems. Health-system pharmacists should establish
a dialogue with group purchasing organizations about the financial implications of the changes associated with this paradigm shift.

**Challenges**

Specialty drug products usually are not an issue for health-system pharmacists when the patient receives the drug at home, even if the patient visits a physician at a hospital outpatient clinic. However, a hospital policy for managing specialty drug products is needed for patients who hope to bring products obtained from specialty pharmacies for administration during visits to the hospital outpatient clinic or during an inpatient stay (Table 3).

Health-system pharmacists may use one of two approaches to brown bagging of drugs with REMS requirements and other specialty drug products when the drug has been dispensed to an outpatient who seeks to have the product administered at a hospital outpatient clinic or as an inpatient. In a “pharmacy-centric” approach, policies and procedures prohibit brown bagging because of concerns about product integrity and institutional liability. The hospital dispenses the drug, even if it has already been dispensed by a specialty pharmacy on an outpatient basis and paid for by the insurance carrier. The hospital bears the cost of the drug, because reimbursement from third-party payers is not available for the same product a second time. To recoup this cost, patients are charged by the hospital for acquiring, dispensing, and administering the product. Providing these drug therapies without capturing these charges is not an option for the hospital using this approach.

In the past, when the number of specialty drug products and the volume of patients receiving these drugs were small and the cost of drugs was not as high, this pharmacy-centric approach had minimal financial impact on hospitals and health systems. However, because most specialty drug products now are very costly and larger numbers of patients are receiving them, this approach places a large burden on the hospital and in turn on the patient.

A “patient-centric” approach may be used to reduce the impact of specialty drug products on patients and hospitals. In such an approach, brown bagging is permitted in certain circumstances under strict protocol. In one approach, specialty drugs are brought to the hospital by the patient (i.e., they are not dispensed by the hospital), and the cost of the drug is borne by the specialty pharmacy. In another, the arrangements are made for delivery of the specialty product directly to the hospital pharmacy, bypassing concerns about product integrity and storage conditions. In either case, the only hospital charge is for administration of the drug (i.e., there is no hospital charge for acquiring or dispensing the drug). The choice between a pharmacy-centric and patient-centric approach to brown bagging often hinges on the institution’s finances, tolerance for liability, and creativity in managing this new paradigm.

Hospitals and health systems (e.g., medical centers with multiple separate facilities) may contemplate establishing their own specialty pharmacy because of the high cost of using outside specialty pharmacies. Key considerations in making this decision include whether the institution is eligible to participate in federal 340B drug discount plans and whether it has an outpatient department eligible to participate as a Medicare Part D sponsor and provider of medication therapy management services. A sufficiently large patient population is required for the business venture to be profitable. Services might be marketed to health systems in the local geographic area to ensure

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Table 6. **Comparison of Traditional and Specialty Pharmacy Supply Chain Models**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Traditional Model</th>
<th>Specialty Pharmacy Model</th>
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<tbody>
<tr>
<td>Patient source of prescription drug products</td>
<td>Outpatient, retail, or mail order pharmacy</td>
<td>Mail order or specialty pharmacy as dictated by payer (specialty pharmacy for drugs with REMS requirements, and specialty pharmacy or physician for compounded products)</td>
</tr>
<tr>
<td>Role of hospital or health-system pharmacy</td>
<td>Purchases drug products (many at a contract price) from traditional wholesalers on volume, cost-minus basis</td>
<td>Purchases drug products (few to none at a contract price) from specialty suppliers on cost-plus-markup basis</td>
</tr>
<tr>
<td>Role of group purchasing organization</td>
<td>Negotiates contract pricing for products and wholesaler agreements, and rebates usually apply</td>
<td>Few or no contract relationships, rebates unlikely</td>
</tr>
</tbody>
</table>

*REMS = risk evaluation and mitigation strategies.*
the fiscal viability of the venture. If the decision is made not to establish an in-house specialty pharmacy, the health system will need to determine whether to use a pharmacy-centric or patient-centric approach and make provisions for some degree of brown bagging.

Recent innovations in technology and therapeutics have increased the numbers of patients who self-administer sterile compounded solutions by i.v. infusion using implantable or external pumps for the treatment of cancer, intractable pain, or chronic illnesses (e.g., pulmonary hypertension) in the home care setting. These patients and their caregivers have learned to use sophisticated drug administration devices and to assume considerable self-care responsibility, similar to the increase in patient responsibility for the management of diabetes mellitus that has taken place over the years. This self-care capability helps patients remain at home, where their quality of life is better than it would be in a hospital. A wide variety of administration devices are available; in some cases, the language in the FDA-approved package insert specifies which specific infusion device must be used. This poses a potential challenge to nursing and pharmacy staff who may be less familiar with a particular administration device than are the patient and the patient's caregivers.

Some sterile products are commercially available, but others must be supplied by a compounding pharmacy (i.e., specialty pharmacy). The expiration dates established for sterile solutions compounded at some of these pharmacies extend beyond those that are customary and accepted in hospital-based compounding practices based on published stability data and USP Chapter 797. In some cases, the evidence supporting the expiration dates, credentials and accreditation status of the compounding pharmacy, safety of compounding practices, and integrity and labeling of compounded products may be questionable.

Hospitalization of a patient who has been self-administering sterile compounded solutions at home can be a challenge for health care providers, especially when the patient or caregivers do not understand why the patient's own solutions cannot be used. Hospital policies and procedures often prevent the patient from bringing such solutions from home, although provisions have not been made for therapies that are available only from compounding pharmacies. Delays in providing therapy and frustration among hospital staff may result from a lack of relevant institutional policies and procedures, uncertainty about the legitimacy of the compounding pharmacy supplying the sterile product, lack of education and familiarity with the features and operation of administration devices, and concerns about the need to provide care consistent with Joint Commission accreditation standards and CMS regulations pertaining to medication integrity and safety. The need to reconcile drug therapies provided in the outpatient and inpatient settings to meet Joint Commission national patient safety goals and the need to take a broad view in evaluating all of a patient's drug therapies instead of focusing on only one provide a strong argument for hospital policies and procedures precluding brown bagging.

**Future of specialty pharmacy**

Spending on specialty drugs amounted to approximately $54 billion in 2008 and is expected to nearly double to more than $99 billion by the end of 2010. Speciality drugs account for 25–30% of the overall medical costs of a health plan. Shifting costs to patients by classifying specialty drugs in a fourth tier represents an initial strategy for health plans coping with the high cost of new therapies. Patient co-payments for fourth-tier specialty drugs can add up to nearly $60,000 a year for an individual receiving multiple products. As additional high-cost therapies are introduced, health plans might consider the use of pay-for-performance and innovative manufacturer contract arrangements for managing the cost of these therapies.

An integrated approach is needed for managing the costs and ensuring the safety of specialty drug products. Components of such an approach might include pharmacy partnerships with specialty pharmacies and home infusion networks for timely product delivery, utilization management to ensure appropriate treatment initiation and adherence, coordination and standardization of electronic billing, and comprehensive data capture and outcomes analysis with online reporting capabilities.

The comparative effectiveness and overall value of specialty drug products are increasingly under scrutiny as health plans and other payers seeking to contain costs make their decisions about coverage. Pharmaceutical manufacturers are devising innovative strategies to ensure that patients have access to their products and that reimbursement is available. Emerging reimbursement models for high-cost pharmaceuticals include risk-sharing agreements between manufacturers and payers, with one-time prepayments for drug therapies based on the overall value of therapy instead of payments for each dose administered.

In the past, many specialty drug products were administered at physician-operated infusion centers. However, rising costs and reductions in reimbursement have caused many of these centers to discontinue services, prompting hospitals and health systems to step in to fill the need for services. Pharmacists in these settings view this as an opportunity to resolve problems with fragmented care by improving communication among physicians and pharmacists.
The survival of hospital-based infusion centers may depend on effective management of the reimbursement process by staff with expertise in reimbursement policies.

Conclusion

The changing paradigm in the supply chain for high-cost pharmaceuticals to permit brown bagging of drug products obtained through specialty pharmacies or other restricted drug distribution systems has important financial and safety implications for patients and health systems. Health-system pharmacists can improve drug safety and manage costs by collaborating with group purchasing organizations, establishing policies for brown bagging, and making efforts to reconcile drug therapy provided in different settings through traditional drug channels and specialty pharmacies or other restricted drug distribution systems.

References

Ensuring drug safety in health systems: Role of the Food and Drug Administration Amendments Act of 2007, risk evaluation and mitigation strategies, and restricted drug distribution systems

Article 204-000-09-006-H03P
Knowledge-based activity
Qualifies for 2.0 hours (0.2 CEU) of continuing-education credit

Learning objectives
After studying these articles, the reader should be able to

1. Discuss the impetus for and drug safety provisions of the Food and Drug Administration Amendments Act (FDAAA) of 2007.

2. Describe the evolution, components, and impact on health-system pharmacists of risk evaluation and mitigation strategies (REMS).

3. Explain the impact of restricted drug distribution systems on patients and health systems, and identify a concern of health-system pharmacists associated with the use of specialty pharmacies and other restricted drug distribution systems.

4. Describe recent trends in the number of drugs with REMS requirements.

5. Describe reimbursement considerations for specialty drugs obtained through restricted drug distribution systems.

Self-assessment questions
For each question there is only one best answer.

1. The FDAAA of 2007 granted the Food and Drug Administration (FDA) authority to
   a. Collect user fees from pharmaceutical manufacturers to pay for postmarketing REMS.
   b. Conduct more robust preclinical drug testing in patient populations likely to use the product.
   c. Regulate specialty pharmacies and other restricted drug distribution systems.
   d. Require postmarketing studies or clinical trials of human drugs and require REMS.

2. Which of the following provided the primary impetus for passage of the FDAAA of 2007?
   a. 2006 criticisms by the Institute of Medicine of FDA for drug withdrawals due to safety problems.
   b. 2006 changes in Joint Commission accreditation standards, with new requirements to ensure product integrity.
   c. 2009 changes in CMS reimbursement regulations for specialty drug products.
   d. Testimony before the U.S. Congress by selected pharmaceutical manufacturers about the limitations of preclinical drug testing.

3. Which of the following factors is taken into consideration by FDA in determining whether REMS are required prior to drug product approval?
   a. The age of the patient population likely to use the drug.
   b. The size of the patient population studied in preclinical drug trials.
   c. The seriousness of known or potential adverse events related to the drug.
   d. The cost of treating adverse events from the drug.

4. REMS assessments may be required
   a. 18 days, 3 months, and 7 months after initial approval.
   b. 3 months, 7 months, and 18 months after initial approval.
   c. 18 months, 3 years, and 7 years after initial approval.
   d. 3 years, 7 years, and 18 years after initial approval.

5. Which of the following provided the impetus for FDA to develop REMS?
   a. 2006 criticisms by the Institute of Medicine of FDA for drug withdrawals due to safety problems.
   b. 2006 changes in Joint Commission accreditation standards, with new requirements to ensure product integrity.
   c. 2009 changes in CMS reimbursement regulations for specialty drug products.
   d. 2009 testimony to the U.S. Congress by selected pharmaceutical manufacturers about the limitations of preclinical drug testing.
CONTINUING EDUCATION

6. The new systematic approach by FDA using data from disparate data sources to monitor the effects of drugs in populations, identify safety problems and the need for drug-use modifications or restrictions, and facilitate an evidence-based approach to adverse drug event monitoring is known as
   a. REMS.
   b. The Adverse Event Reporting System.
   c. The MedWatch program.
   d. The Sentinel Initiative.

7. Which of the following formats for risk minimization action plans (RiskMAPs) provides the greatest safeguards?
   a. Continuing-education programs for health care providers.
   b. Informed consent forms for patients.
   c. Performance-linked access systems.
   d. Reminder systems.

8. Which of the following statements about the elements to ensure safe use of drugs with known serious risks as part of REMS is correct?
   a. The elements are required for all drugs with REMS and may include special training or certification for prescribing or dispensing only under certain circumstances, special monitoring, or use of patient registries.
   b. The elements are required for some (but not all) drugs with REMS and may include medication guides, patient package inserts, or communication plans for health care providers.
   c. Reclassifying over-the-counter drugs with REMS to “behind-the-counter” status.
   d. Standardizing REMS as part of established drug procurement systems.

9. Which of the following is the most serious concern associated with the development of REMS for extended-release opioid analgesics?
   a. Conflict with medical board pain management continuing-education requirements.
   b. Potential for delays in providing patient care.
   c. Increased cost of drug therapy.
   d. Misuse, abuse, or accidental overdose of the drugs.

10. Which of the following was addressed in the FDA final rule issued in 2009 requiring new warnings and related labeling for over-the-counter analgesic, antipyretic, and antirheumatic drugs?
   a. Warnings about stomach bleeding from aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) and severe liver toxicity from acetaminophen.
   b. Warnings about stomach bleeding from aspirin but not NSAIDs and severe liver toxicity from acetaminophen.
   c. Warnings against the use of aspirin during pregnancy and breastfeeding.
   d. Warnings against the use of aspirin, warfarin, and alcohol in any combination during pregnancy and breastfeeding.

11. Which of the following approaches is advocated by the American Society of Health-Systems Pharmacists to minimize the burden of FDA REMS requirements on health-system pharmacists?
   a. Integrating REMS into the MedWatch program.
   b. Educating members of medication-related committees and pharmacy, medical, and nursing staffs about FDA REMS requirements.

12. Which of the following most directly reflects current FDA requirements of pharmaceutical manufacturers for drug safety?
   a. REMS.
   b. Restricted drug distribution systems.
   c. RiskMAPs.
   d. Specialty pharmacies.

13. Which of the following statements about REMS and restricted drug distribution systems is correct?
   a. REMS may involve restricted drug distribution systems, but restricted drug distribution systems are not necessarily used for drugs with REMS requirements.
   b. REMS and restricted drug distribution systems are used only for drugs covered under Medicare Part B or D.
   c. All drugs with REMS requirements are handled through restricted drug distribution systems.
   d. Drugs are handled through restricted drug distribution systems only if they are subject to REMS requirements.

14. Which of the following drugs is among the earliest supplied through a restricted drug distribution system?
   a. Clozapine.
   b. Infliximab.
   c. Natalizumab.
   d. Romiplostim.

15. The recent shift from a traditional supply chain model to a specialty pharmacy supply chain model for high-cost pharmaceuticals has the potential to
   a. Increase costs for health systems because of the negotiation of contract prices and rebates.
b. Increase costs for health systems because of purchasing on a cost-plus-markup basis.  
c. Decrease costs for health systems because of the negotiation of contract prices and rebates.  
d. Decrease costs for health systems because of purchasing on a volume, cost-minus basis.  

16. Which of the following can play the largest role in coordinating traditional and specialty pharmacy drug purchasing contracts and distribution channels?  
a. CMS.  
b. FDA.  
c. Group purchasing organizations.  
d. Pharmaceutical manufacturers.  

17. Which of the following is a potential advantage for health systems of a patient-centric approach to brown bagging drug products obtained from specialty pharmacies compared with a pharmacy-centric approach?  
a. Greater patient safety.  
b. Less uncertainty about product integrity.  
c. Lower cost.  
d. Lower institutional liability.  

18. Potential problems for health systems associated with permitting brown bagging of compounded sterile products used with implantable or external infusion pumps include a lack of nurse and pharmacist familiarity with the proper operation of infusion devices.  
a. True.  
b. False.  

19. In recent years, the number of drugs with REMS requirements has  
a. Increased because of a greater concern among pharmaceutical manufacturers about product liability.  
b. Increased because of a greater commitment of the FDA to postmarketing surveillance and drug safety.  
c. Decreased because of more extensive preapproval clinical testing of new drugs.  
d. Decreased because of greater use of restricted drug distribution systems.  

20. A fourth tier for specialty drug products has been created by some health plans to:  
a. Ensure the capture of charges for high-cost drugs.  
b. Improve drug safety.  
c. Reduce the cost of drugs through volume discounts.  
d. Shift a larger portion of the cost of some drugs to the patient by increasing the copay significantly.  

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