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ISMP
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Acute Care
ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

Proper deployment of REMS to reduce potential drug-related harm and medication errors—Part I

Problem: Risk Evaluation and Mitigation Strategy (REMS) programs were first instituted by the US Food and Drug Administration (FDA) in 2007 to ensure the benefits of a medication with serious safety concerns outweigh the risks.[1] REMS programs include one or more of the following components designed to reinforce intended medication-use behaviors and actions that support safe use: (1) patient information (e.g., medication guide), (2) a communication plan, (3) elements to assure safe use (ETASU), and (4) an implementation system. ETASU may include certification of prescribers or dispensers, drug administration restricted to certain healthcare settings, specific monitoring requirements for patients, and/or enrollment of patients in a registry.[2,3] REMS programs also have a timetable of assessments of when the manufacturer will provide reports to the FDA to evaluate the effectiveness of the REMS components.[1,2]

There are approximately 60 medications that currently have REMS requirements. In December 2021, FDA launched the REMS Public Dashboard (www.ismp.org/ext/1112) to expand efficient access to data and report-generating capabilities of REMS programs for healthcare providers, research organizations, academia, industry, and others.

While REMS programs are intended to mitigate risk, the number of different programs and databases, wide variety of program requirements, scarcity of implementation tools, and lack of organizational resources have sometimes made it difficult for frontline practitioners to meet the requirements of the various programs. Institutions may face other challenges, some of which are highlighted below, based on reports we have received.

REMS-related problems reported to ISMP

Failing third-party REMS audit. Vigabatrin, an antiseizure medication used to treat infantile spasms and refractory complex partial seizures, carries a Boxed Warning for the risk of permanent vision loss. For inpatient pharmacies to dispense vigabatrin, they must be enrolled in the REMS program, and staff must be trained in the program requirements. Staff must verify that the prescriber is certified in the program and that the patient is enrolled in the program. Staff must obtain authorization to dispense the drug by contacting the program by phone or logging in online (www.ismp.org/ext/1088). Staff must also document the prescriber identification (ID) number, patient ID number, and the authorization code that are all assigned by the Vigabatrin REMS Program, in a paper/digital logbook or in the electronic health record (EHR) within 15 days of the patient's admission.

In a case reported to ISMP, an inpatient pharmacy was audited for compliance by a third party on behalf of the Vigabatrin REMS Program. The initial audit consisted of reviewing over 60 unique orders spanning one calendar year. While completing the self-evaluation portion of the audit, the pharmacy found that just over 10% of the orders had the patient ID number documented in accordance with the program requirement. This finding prompted subsequent focused audits of certain patient profiles by the third party, and ultimately the pharmacy did not pass the audit.

The pharmacy department noted there was not a standard method for documenting the patient ID, which made it difficult to locate this information. The patient ID was found in a variety of locations, including notes fields in order verification software (e.g., order comments, pharmacy

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Alcohol can remove label information. Over the years, we have received several reports in which certain inks on labels of injectable medications were smeared or removed when wiped with disinfectant products. Most often the expiration dates and lot numbers were smeared or removed when the vials were wiped with alcohol prior to being brought into a sterile environment (**Figures 1**, **2**, and **3** [on page 2]). This may contribute to staff unknowingly preparing a dose from an expired vial or not being able to identify a lot number for documentation after preparing the drug. In some cases, if the expiration date and lot number cannot be confirmed, the medication may need to be discarded.

Figure 1. Alcohol-smeared label information on Cumberland Pharmaceuticals' **CALDOLOR** (ibuprofen) injection vials.

Figure 2. Pharmacy staff were unable to confirm alcohol-smeared expiration date and lot number on Sandoz's piperacillin-tazobactam vials.

We have contacted the US Food and Drug Administration (FDA) to recommend that manufacturers evaluate the ink used on their products to ensure label information will not

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comments, alert history documentation) and notes in patient care documentation (e.g., physician notes, social work notes). The pharmacy was placed on a corrective action plan by the Vigabatrin REMS Program auditors (without guidance on how to operationalize the requirements), and follow-up audits were scheduled in order for the organization to maintain the ability to prescribe and dispense vigabatrin.

Inappropriate prescribing of fentaNYL citrate oral transmucosal lozenge (ACTIQ). Actiq is indicated for the management of breakthrough pain in cancer patients 16 years and older who are opioid-tolerant. For inpatient pharmacies to dispense Actiq, the pharmacy must be certified and enrolled in the Transmucosal Immediate Release Fenta**NYL** (TIRF) REMS Program, and staff must be trained in the program requirements. Inpatient pharmacies must develop policies and procedures to ensure that inpatients who require a TIRF medicine are opioid tolerant. While providers who prescribe TIRF medicines for outpatients are required to enroll each patient into a registry and document opioid tolerance with every outpatient prescription for a TIRF medicine, in the inpatient setting, healthcare providers are not required to enroll in the TIRF REMS program.

A pharmacist reported three separate occasions in which inpatient prescribers attempted to order an agent to treat sore throat and searched "lozenge," and inadvertently prescribed Actiq. Fortunately, in two of these cases, a pharmacist identified that the patient did not have a disease state necessitating TIRF and contacted the provider for correction. In the third case, the prescriber immediately recognized their own error. In each of these cases, the patients had not been taking other opioids and were therefore opioid-naïve. The pharmacist noted a need to update the policy and procedure to limit the ability to prescribe TIRF products only under formulary restrictions (e.g., continuation of home therapy, cancer diagnosis) and to certain providers (e.g., Pain Management Specialist, palliative care practitioner, hematologist/oncologist) to prevent patient harm.

Safe Practice Recommendations: Organizations such as the American Society of Health-System Pharmacists (ASHP) have advocated for a centralized electronic REMS system to help practitioners manage the various program registrations, provider education, and patient documentation requirements since 2015 (www.ismp.org/ext/1113). ISMP is in support of this statement and also calls upon EHR vendors to design systems to better manage REMS requirements. Organizations should consider the following recommendations:

Assign a REMS coordinator. Pharmacy departments should designate an individual responsible for identifying formulary medications with REMS programs that are dispensed within the hospital. The coordinator should be responsible for enrolling the organization in REMS programs, identifying any changes to the REMS requirements, maintaining a list of authorized prescribers, educating staff, and demonstrating compliance through routine audits. In addition, to ensure consistency of REMS management in the absence of the REMS coordinator, consider cross-training staff.

Assess REMS requirements upon initial Pharmacy & Therapeutics (P&T) review. P&T committees should proactively (and retroactively) conduct a risk assessment of clinical and operational requirements for REMS medications that may be added to, or are already on, the formulary. Based on the assessment, this may involve limiting access to REMS medications to "no new inpatient starts" or "home supply only."

Develop a policy and procedure for REMS programs. Develop a policy listing all formulary-approved medications with REMS requirements and outlining the requirements. This policy should include educational requirements, competency assessments, and procedures for prescribing, dispensing, and administering each medication. The policy should be updated every time a new medication with REMS requirements is added to the formulary. Document review of this policy on an annual basis. Consider creating a REMS resource binder (electronic and hard copy) that staff can access to find program requirements, even in the event of planned or unplanned computer downtime.

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be altered when exposed to standard cleaning procedures. Notify staff of this risk and always check critical label information before using any product. If smearing does occur, be sure to report this to the manufacturer and ISMP.

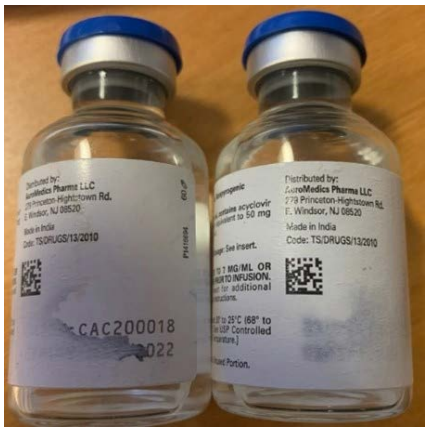

Figure 3. Vials of acyclovir from AuroMedics with alcohol-smeared, illegible lot numbers and expiration dates.

HIGH-ALERT

Fluorouracil injection may precipitate. A hospital received 11 vials of fluorouracil 2.5 g/50 mL (50 mg/mL) injection (NDC 63323-0117-51, lot 6129520) that contained precipitate. When they reached out to the manufacturer, Fresenius Kabi, they were informed that the precipitate can be redissolved by placing the vials into a water bath at 140 degrees Fahrenheit (60 degrees Celsius), shaken, then allowed to cool to body temperature before preparing a dose. Otherwise, the vials can be returned to the company.

We reached out to Fresenius Kabi and were informed that fluorouracil 50 mg/mL is a super-saturated solution, and potential precipitation at low temperatures is a well-known and documented phenomenon. The labeled storage temperature is 68 to 77 degrees Fahrenheit (20 to 25 degrees Celsius). The manufacturer's internal testing showed that fluorouracil might precipitate if left at lower temperatures, and re-solubilizing the product as directed in the United States Pharmacopeia (USP) product monograph has no negative effect on product characteristics and formulation. However, there is only data to support heating to re-solubilize the product once. The company has reviewed their batch record documentation and inspected reserve samples of the lot reported and found no evidence of any

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Build ETASU directly into the EHR. Consult with information technology teams to build required fields into the EHR, such as patient ID, prescriber ID, authorization codes, and/or relevant laboratory data. Build in clinical decision support to notify practitioners that they are prescribing, dispensing, or administering medication with REMS program requirements. Ensure that reports may be easily generated for auditing purposes. Establish criteria regarding where and for how long REMS compliance documentation must be maintained to meet the REMS requirements.

Limit prescribing to program-certified prescribers. Only allow REMS-certified practitioners to prescribe medications that have this REMS program requirement. If possible, build in a prompt in the EHR requiring a prescriber to enter their prescriber ID to continue placing the REMS medication order. The REMS coordinator should maintain a list of program-certified prescribers.

Educate staff and provide resources. Given the number of existing REMS programs, it is impractical for staff to remember the requirements for each individual program. To optimize compliance, education should focus more on cues (i.e., flagging that a medication falls under the REMS category in the EHR) and knowing what resources (e.g., REMS policy, REMS resource binder) are available to comply with program requirements.

Identify barriers to obtaining REMS medications. Identify if REMS medications are available from your routine distributors and wholesalers, if the medication is a Limited Distribution Drug (LDD), or if there is a need to contract with specialty pharmacies and distributors. Monitor usage and supply levels to ensure enough medication is on hand to avoid unexpected shortages and treatment delays. To prevent a disruption in care post-discharge, consider potential barriers the patient may face when obtaining the REMS medication for outpatient dispensing (e.g., ensure prior authorization if applicable).

Develop a system to ensure the delivery of patient information. Institute protocols for inpatient orders and outpatient prescriptions (e.g., automatic printout) to ensure that mandatory patient information, such as medication guides, are distributed to the patient when a medication with a REMS program is dispensed or administered.

Conclusion

ISMP recognizes the value of REMS programs to educate and/or reinforce actions to reduce the frequency and/or severity of adverse effects associated with medications. However, the often complex and time- and labor-intensive nature of these programs may have unforeseen consequences. We plan to publish a follow-up article, **Part II**, describing how a health system was able to operationalize REMS program requirements into their systems and processes.

References

1) Risk evaluation and mitigation strategies: REMS. US Food and Drug Administration. Accessed January 3, 2023. www.ismp.org/ext/1089
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3) Prescribers' Digital Reference (PDR). REMS Summary of Terms. Accessed February 6, 2023. www.ismp.org/ext/1178

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manufacturing-related issue that would be a cause of elevated levels of precipitation. All finished product testing and documentation requirements for release were met.

Organizations and practitioners should be aware that, similar to mannitol crystallization, fluorouracil precipitation can occur at low temperatures. Store fluorouracil per the package insert (i.e., room temperature). Before preparing fluorouracil, staff should visually inspect each vial to ensure it does not have observable particulate matter or precipitate. Precipitate is typically white and flaky. Unlike precipitate, particulate matter will not dissolve. If your organization has the means to heat the vial to dissolve the precipitate as outlined by the manufacturer, develop a process to document when this has been done. Also, ensure that each vial is only heated once, or contact Fresenius Kabi to return the vials. If there are any concerns that a vial may have particulates, do not use the vial and contact Fresenius Kabi to report the issue to the manufacturer. Also report any issues to the US Food and Drug Administration (FDA) and ISMP.

Special Announcements

ISMP/ECRI shortages survey reminder

We are conducting a short survey on the continuing crisis with **drug shortages and supply chain disruptions**. Please take a few minutes to complete this survey by **July 27, 2023**, by visiting: www.ismp.org/ext/1195. We appreciate your participation!

Foundations in Medication Safety

ISMP's new online, interactive course offers healthcare organizations a standardized, cost-effective way to ensure staff involved in the medication-use process have the basic knowledge they need. For details, visit: www.ismp.org/node/74900.

Nominations open for CHEERS Awards

Nominations for this year's **CHEERS Awards** are now open and will be accepted through **August 6, 2023**. For more information, visit: www.ismp.org/node/123.