Challenges of Integrating REMS Elements into Pharmacy Systems

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Introduction

The development of specialty drugs is a growing trend in the pharmaceutical industry, necessitating the advancement of pharmacy management operations, as the indicated diseases tend to be more complex and require greater care management. In order to assist with managing these specialty drugs, the Food and Drug Administration (FDA) implemented Risk Evaluation and Mitigation Strategies (REMS). The program has meaningfully benefited patients suffering from diseases, as without the REMS program, their desperately needed treatment options may have never been approved. However, the effectiveness of the REMS program has been argued and studies reveal limited effectiveness due to challenges faced. Current overall oppositions to the REMS program are the high indirect costs to the health care system, the increased stringent guidelines being placed on the drugs, and the access to care.

As this paper will demonstrate, the effectiveness of the REMS program can be increased by standardizing REMS elements and utilizing configurable pharmacy management tools, thus decreasing the current burden on the pharmacy, and subsequently the entire healthcare system.

Background

History

Created by the Food and Drug Administration Amendments Act (FDAAA) in 2007, REMS combatted the FDA’s lack of authority to manage risks carried by certain drugs post approval. The FDA currently can only extract voluntary commitments as their authority postapproval extends only to the suspension or withdrawal of a license. The goal of the program was to enable drugs that bear a significant risk to enter the market due to the benefit to the patient; while not being “unduly burdensome on patient access” and minimizing “the burden on the health care delivery system.” Due to the varying nature of the REMS requirements, the weight of the program can be felt by all REMS stakeholders, including payers, pharmacists, distributors, regulators, providers, life sciences companies, and patients.

Specialty Drugs

Specialty drugs are categorized as almost all self-administered oral and injectable medications, with approximately seventy percent involving inflammatory conditions, multiple sclerosis, cancer, and HIV. Additionally, specialty pharmaceuticals are characterized by a high cost per patient and usually require unusual or resource-intensive dispensing processes that require clinical management. Of the patients that are using specialty drugs, thirty percent receive the medication from a specialty pharmacy, twenty one percent from a drugstore, ten percent from a doctor’s office, eight percent from an outpatient clinic, six percent from a mail-order pharmacy, and twenty-two percent from a combination of sites. Specialty pharmacies such as Walgreens, CVS Caremark, and Prime Therapeutics Specialty Pharmacy provide care management services above and beyond those of retail pharmacies. For example, Prime must qualify to distribute a drug by meeting laborious obligations such as benefit investigation services, prior authorization support, and shipment tracking. These specialty pharmacies are distinctively equipped to care for these types of patients.

REMS

Components

Due to the nature of the diseases that specialty drugs are intended to treat and the associated risks, more are being approved with REMS. Currently, seventy four drugs have REMS attached to them, as well as four classes of drugs. REMS typically includes three main sections: a timetable for submission of assessments, additional safety elements, and Elements To Assure Safe Use (ETASU). In order to determine which drugs will be approved with REMS and the extent of the coverage, the FDA analyzes the size and demographics of the intended
population, the seriousness of the disease, the expected benefit, the seriousness and incidence of any adverse events, and whether it is a new molecular entity.\textsuperscript{14} The majority of REMS programs require safety communication to health care professionals, patients, or both; but can also include patient, pharmacy, and prescriber registries, as well as a limited distribution network.\textsuperscript{15} Required communications include prominent warning language, such as a Boxed Warning, a Medication Guide, a Patient Package Insert, a “Dear Healthcare Professional” letter, and modernized risk advisory information for the media.\textsuperscript{16}

A medication guide is the most common form of a REMS requirement and describes potentially serious public health concerns; while another option is a patient package insert that is provided in order to mitigate any serious risks.\textsuperscript{17} A communication plan is another common requirement that distributes information about REMS elements, describes safety protocols, and shares information with health care providers.\textsuperscript{18} ETASU are more extensive and typically require additional steps to be taken by all parties, such as training and certifications, tests, and paperwork before access to the drug is granted.\textsuperscript{19}

**ETASU**

Physicians, pharmacists, and patients are typically required to do little to obtain access to a REMS drug, but drugs with ETASU create a larger burden on all parties. ETASU is applied to drugs that are significantly beneficial for the patient, but are associated with serious adverse drug experiences; or if other REMS elements are considered inadequate to mitigate serious risks.\textsuperscript{20} A typical requirement of ETASU is that healthcare providers and/or pharmacists must be trained and/or certified, as well as certifying the actual dispensing location.\textsuperscript{21} To track certifications, patients, pharmacies, and physicians may need to be enrolled in a registry.\textsuperscript{22} Another burden to comply with is the that the drug may only be dispensed to a patient with evidence of safe use conditions, such as lab tests, which requires all three parties to complete additional steps.\textsuperscript{23} The ETASU Implementation System monitors and evaluates the execution of the ETASU requirements.\textsuperscript{24} Only five of the drugs approved with ETASU do not require an Implementation System.\textsuperscript{25} Additionally, pharmacies could be audited to ensure that medication guides are distributed, additional data elements are collected, or that additional educational elements are completed, per the Implementation System.\textsuperscript{26}

Table 1: REMS Programs with Requirements shows the sum of different REMS requirements across all approved REMS drugs. The analysis conducted revealed that fourteen of the approved REMS drugs only require a Medication Guide and nothing else, while almost half of the approved REMS drugs require ETASU.\textsuperscript{27}

<table>
<thead>
<tr>
<th>Shared System</th>
<th>Medication Guide</th>
<th>Communication Plan</th>
<th>Elements to Assure Safe Use</th>
<th>Implementation System</th>
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<td>6</td>
<td>36</td>
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Of the forty drugs approved with extensive ETASU requirements, seventeen also require a Medication Guide and seven require a communication plan, as seen in Table 2.\textsuperscript{29}

<table>
<thead>
<tr>
<th>Medication Guide</th>
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<td>17</td>
<td>7</td>
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Benefits

While the creation of the REMS program does necessitate additional work across the healthcare system, there are several worthwhile benefits. Through this program, many patients are granted access to life-saving treatments that would otherwise not be approved. Some have argued that manufacturers use REMS to block competitors’ entry to the market, but this is unfounded as the goal of the REMS program is not to limit product indications, only to mitigate the correlated risks. The FDA is developing a qualitative evaluation grid containing five factors that will be applied to all drugs, not just REMS drugs, vying for commercial approval. Thus, in addition to REMS products facing sensitive risk/benefit analysis, they also face a heightened market risk. In order to enter the market, REMS is necessary for these drugs to protect and improve the treatment of patients. Further improvements in REMS patient care have been demonstrated by the unique covenant between patient and pharmacist.

Challenges Faced by REMS

Lack of Standardization

The lack of standardization of REMS is the greatest challenge currently faced by the industry. REMS requirements are evaluated on a case by case basis which negates almost any attempt for standardization. Due to this process, the format and information contained in all REMS elements lack formal standardization. For instance, the requirements of when to dispense a Medication Guide is formalized, but not the overall format and content. The lack of standardization makes it difficult for document integration into healthcare systems. This standardization is imperative for all REMS drugs and for retail, specialty, and hospital-based pharmacies. The industry is anxiously awaiting the FDA’s draft guidance targeting REMS standardization which is anticipated to alleviate current burdens.

Operational Inefficiencies

The lack of standardization of REMS elements translates into systemic operational inefficiencies. Drugs with ETASU that require dispensing restrictions can force physicians and pharmacists to obtain certifications prior to dispense and for patients to complete mandatory tests. Both of these tasks could cause delays to patient treatments, and must be completed within a mandated timeframe. Pharmacists must also be able to identify patients at a greater risk of harm and consequently deliver a greater volume of services. Implementation Systems also require many electronic tasks that cannot be completed on standard software. Operational inefficiencies are caused by the lack of interoperability across systems and devices that need to exchange and interpret shared data. Studies have shown that trying to implement new REMS systems can take anywhere from three weeks to three months per program as each is unique, with an additional one hundred sixty hours of pharmacy workload.

Compliance

These operational inefficiencies translate into the overall burden of compliance for the physician, patient, pharmacy, even the drug manufacturer. The first obstacle that must be overcome is the determination of who is responsible for each REMS activity as it is often unclear. Some requirements for biologics are extensive and patient-specific which necessitates complicated coordination across all care-givers. While pharmacists are trained in advanced pharmaceutical care, they cannot always be relied upon to complete these practices. For instance, it is not standard practice for community pharmacists to conduct routine follow-ups of patients that receive a new prescription, yet this may be critical for a REMS patient. Therefore, patients can be exposed to unnecessary risks due to non-compliance with FDA standards at several points-of-care; thus failing the intended goal of REMS to prevent adverse events. Furthermore, previous attempts to improve efficiency by making REMS drug information available at the point-of-care have failed and actually caused additional barriers to
compliance, as it is impractical to integrate all of the DEA and medical compliance information at these points.\textsuperscript{47} It is also hypothesized that manufacturers have not felt the full brunt of their inability to comply with REMS requirements as most cases filed after the initiation of REMS have failed to proceed through the regulatory and legal systems.\textsuperscript{48}

\textit{Burden on the Pharmacy}

As most of the coordination of care has fallen to the pharmacy, it bears the greatest burden. Traditional pharmacy workflow follows a linear path, which becomes convoluted if REMS steps are added in.\textsuperscript{49} Pharmacies must help with supplemental communication plans, provision of required medication guides, validating that the patients and physicians are enrolled in a REMS registry, and that their pharmacists are certified via training.\textsuperscript{50} The pharmacist may also be required to provide patient consultations for every fill, obtaining and maintaining confirmation and authorization numbers that often have specific time limits, tracking each dispense for quantity restrictions, and ensuring that appropriate documentation is received and validated.\textsuperscript{51} In order to assist with these requirements, pharmacies often employ data management systems to guarantee compliance, but many systems cannot support all of the requirements.\textsuperscript{52} Pharmacies cannot be expected to take on additional responsibilities without being compensated further.\textsuperscript{53}

\textbf{Solutions for Unburdened Integration}

\textit{Standardization}

There is currently an FDA pilot program focusing on structured product labeling (SPL) in order to finalize a standard format for REMS.\textsuperscript{54} The program’s goal is to integrate REMS into electronic health records (EHRs), which will reduce the workflow burden on both physicians and pharmacists.\textsuperscript{55} SPL is a data standard that is used for marketing applications to capture and share information about the drug.\textsuperscript{56} The new standards are anticipated to provide guidance on a structured prototype for REMS, a code set, and an implementation guide.\textsuperscript{57} Standardizing the format and content of REMS will help to determine who is required to carry out the requirements, what the activities are, when activities must be completed, and contain references to additional materials.\textsuperscript{58} Once REMS requirements are standardized, they can be smoothly integrated into current workflows, thus reducing the overall burden. These standards will eventually lead to certified vendor solutions, such as United BioSource Corporation or HealthBridge, which are currently leveraged to assist with REMS.\textsuperscript{59}

\textit{Pharmacy Systems}

Healthcare systems are evolving towards flexibility, value generation, patient-centeredness, and responsiveness to the context of care.\textsuperscript{60} Health information technology also aims to deliver “just in time” updates on drug warnings, provide prompts for patient counseling, and reminder systems, all of which are imperative to the support of a REMS program.\textsuperscript{51} The ability to customize a computerized system to facilitate workflow for both physicians and pharmacists will be key. One such system already utilized by a majority of the specialty pharmacy network is ScriptMed\textsuperscript{TM} Enterprise, which provides the necessary flexibility in support of REMS programs.\textsuperscript{62} The system allows for the tailoring of computerized order entry screens, clinical decision support, user prompts, validation of assessments, and order tracking, all fundamental facets of system engineering.\textsuperscript{63} The configurable aspects of the system act as a process management tool by controlling work queues and electronic reminders.\textsuperscript{64} The tool also allows for the creation of registries, data collection, and provides reporting functionality from the pharmacy to the drug manufacturers.\textsuperscript{65} Pharmacy management tools that are able to support all unique REMS requirements will be crucial to unburdened integration into existing and evolving healthcare systems.
Certain ETASU requirements have obligations that most would not expect to be managed by current pharmacy systems on the market. Actelion’s drugs Tracleer and Opsumit contain requirements that force pharmacies to function outside of their routine workflow. Celgene also has three REMS drugs with ETASU that require strict timing, authorization and confirmation numbers, and quantity restrictions that can be extremely challenging for a specialty pharmacy to manage. Biogen’s Tysabri also contains ETASU requirements that compel pharmacies to build custom integrations to integrate with their dispensing sites. All of these programs have the potential to be supported by pharmacy systems such as ScriptMed™ owing to the configurable nature of the tool. Pharmacy tools that can support atypical requirements will greatly ease the burden on pharmacists.

In addition to having certified vendors for specialty pharmacy management systems, the ability to integrate REMS documents into EHRs will also be crucial. EHRs, coupled with clinical management, can improve the effectiveness of disease-management models. The growing trend in the industry of also integrating with mobile-health apps for patients can help patients schedule visits or the necessary lab tests to remain compliant with REMS.

**Data Sharing**

As more systems support REMS, the data sharing aspect will also serve to increase the integration of REMS with healthcare systems. The FDA has several examples of data sharing programs, such as the Mini-Sentinel System, that have proven to be successful. An example of a closed system that shares data across entities is Kaiser, as it contains a health plan, a hospital system, and a medical group. This example is unique as it is a closed system and does not work as well if a participant has to go outside the system. However, it has shown to be very efficient as users can view the EHRs, which helps to ensure that REMS requirements such as lab results and clinical factors are met. The data sharing capabilities demonstrated by this system indicates that pharmacists with direct access to clinical services will counsel treatment plans, screen for interactions, and assist with finances far more effectively as it cuts down on time delays and barriers to data access. Therefore, data analytics would result in better care coordination as all of the patient information would be readily available, which could prevent adverse events or keep a patient on-therapy. As adverse drug events are severely underreported, having the data stored and shared has untapped potential for all involved parties.

**Consolidated Guidelines for Classes of Drugs**

Along with standardizing REMS, the recent movement of creating similar guidelines across classes of drugs has proven to be effective. For example, TIRF (transmucosal immediate-release fentanyl) allows for an FDA approved use of a “switch” which ensures greater compliance as the pharmacies do not have to obtain an approval of the claim. A more recent development is the class-wide REMS program for long-acting opioids that encompasses prescriber education for patient management and other informational materials. The development of this class-wide REMS was developed as a result of Obama’s administration’s concern about overdoses. If the FDA can continue to implement class-wide REMS, it will help to set drug manufacturer’s expectations during drug development, but will also help to streamline physician and pharmacy workflow. Conversely, there are multiple in-class REMS that have different requirements as they were written by individual manufacturers. When this occurs, it increases the administrative burden by confusing pharmacists and negating the goal of standardizing and streamlining overall class REMS requirements. Once these programs are updated, it is hypothesized that overlaying standardized class-wide REMS on top of the anticipated SPL changes will greatly improve efficiency to the pharmacies.
Conclusion

Overall flexibility is integral to the sustainability and success of the REMS initiative. Pharmaceutical history has shown that by standardizing the approach to an industry-wide challenge, efficiency gains and greater patient care can be generated, similar to the creation of electronic prior authorizations. Once the industry has standardized REMS requirements, utilizing pharmaceutical management tools will greatly ease the burden on pharmacies and enable the integration of complicated ETASUs into the patient care management model. Consequently, certified vendor solutions will then increase the data sharing across health technology systems, as well as with the drug manufacturer. As specialty drugs continue to grow, so will REMS and the need to smoothly integrate the requirements into the patient’s care coordination.
Notes


3 Projects, Implications, 268.


5 Projects, Implications, 268.

6 Dorfman, Regulation.


8 Monroe, Integrated, 334.

9 Barlas, Networks, 123.

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15 Ibid.

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