STREAMLINING RISK EVALUATION AND MITIGATION STRATEGIES (REMS) THROUGH INNOVATIVE INTEGRATION: A COMPREHENSIVE WHITE PAPER

This paper delves into the evolution of Risk Evaluation and Mitigation Strategies (REMS) with elements to assure safe use (ETASU) over the last 15 years. Despite significant advancements, the burden placed on stakeholders such as prescribers, pharmacies, and patients remain an ongoing and constant challenge. This paper investigates the root causes of these challenges and explores the potential of integration and innovation to alleviate the burdens associated with REMS and thereby improving safe access to these important therapies. It introduces a groundbreaking strategic solution developed jointly by Shepherd Safety Systems and Invaryant Inc. that promises to introduce thoughtful and effective change to REMS programs by seamlessly integrating them into stakeholders' clinical workflows, while effectively supporting safe use by patients.

In their 15-year history, Risk Evaluation and Mitigation Strategies (REMS) with elements to assure safe use (ETASU) have evolved significantly, but one fact has never changed—they are burdensome for the prescribers, pharmacies, patients, and other stakeholders who must fulfill REMS requirements to get treatments to the patients who need them.

The common thread in the burden felt by various REMS stakeholders is that fulfilling REMS requirements necessitates stepping outside of their daily routine, as well as the systems that support those routines1. For example, prescribers must leave their electronic medical record (EMR) system, where they manage patient records, messaging, and prescriptions, and go to a REMS program's website with a unique login to complete the REMS obligations that stand between patient and drug. Also, the reminders for those REMS obligations often go to email, further exacerbating the prescriber's already heavy workload of paperwork and administrative responsibilities. Stepping outside the prescriber's workflow often translates to delays in fulfilling REMS obligations because those obligations are out of sight and therefore out of mind.

On a similar note, the challenges with using individual program websites lead many prescribers to resort to more manual processes, like paper forms and fax machines. Prescribers typically do this because it's easier to have office staff complete information on paper forms for the prescriber to simply sign, as opposed to the prescriber completing all the required information by logging into a website. While this is perceived as easier by many prescribers, it is much more costly for manufacturers operating REMS programs because of the call center staffing levels necessary to process faxes into the REMS system, as well as to address calls from stakeholders to resolve issues or pose questions.

The situation is no better for pharmacies that handle REMS drugs because they typically cannot access the internet (and therefore REMS websites) from within their pharmacy management system (PMS), which is the system where they complete their work each day. To further complicate the matter, some pharmacies do not have the ability to access the internet at all from their pharmacy computer, while others do not have email addresses that they can use to create REMS website login credentials.

REMS INTEGRATION & INNOVATION

An excerpt from CDER's 2022 Annual Report

- Completion of REMS requirements are often done outside of stakeholders' clinical workflows.
- In some cases, manual processes are used, which can be costly and time-consuming for prescribers and pharmacists and can create delays or barriers to medication access for patients.
- Each REMS program is slightly different, which can make it difficult to exchange information across REMS systems, electronic health records, and pharmacy information management systems.

Regardless of the reason for the out-of-workstream burden, at the end of the day, it's the patient that pays the highest price for REMS burden—potential delays in getting the treatment they need[2]*.* While REMS professionals recognize improvements are needed to provide the broadest possible patient access to REMS drugs, such efforts have either fallen flat or not significantly decreased burden or improved access outcomes.

Take the insurance claims network (i.e., the switch) for example; about eight years ago, it was believed that putting REMS information for pharmacies into the switch was the silver bullet for the burden pharmacies felt when dealing with REMS drugs. Today, the vendor that was providing REMS services via the switch has left the REMS space, and products that once leveraged that system are back to unique login websites[3].

In another effort to make REMS less burdensome, some REMS programs have redesigned their approach to safe use requirements by introducing a patient status form. The intent of patient status forms is to take frequent requirements, like submission to the REMS of lab results or patient monitoring outcomes and simplify them into a single form. The intent was good; the outcome, not so much. Across many REMS programs, patient status forms are the top driver of REMS operating expenses because of outbound calls necessary to track down overdue forms and manual processing of faxed-in, handwritten forms. The cost is simply a biproduct of a bigger problem—patient status forms are far outside of the daily routine of most prescribers.

While the lessons learned regarding REMS burden are many, it is not time to abandon hope. FDA recognizes that getting REMS requirements into stakeholders' workflows is tantamount to reducing REMS burden and increasing REMS success, as demonstrated by their support of HL7 CodeX REMS Use Case[4] and a recent FDA website post about REMS modernization opportunities[5]. These efforts to improve REMS are the culmination of years of discussion at REMS conferences and among REMS Industry Consortium (RIC) members about leveraging technology to improve REMS.

With over 30 years of combined REMS experience, the leadership team at Shepherd Safety Services has seen first-hand that REMS technology is only as good as the REMS strategy that goes with it. Shepherd believes that strategy is the foundation of REMS success, but a REMS strategy must include robust implementation and operation tactics that address the realities of the complex US healthcare delivery system. With that in mind, Shepherd evaluated a variety of emerging players in both the REMS and healthcare technology spaces to find a solution-provider who could improve upon the currently offered technologies for REMS operations, which are largely outside stakeholders' workflows.

While many companies understand ways that technologies could be used to access stakeholders in their native environments, the challenge was

finding a company that also understood the business challenges that underpin implementing such technologies. For example, in the US we still have more than 400 EMR providers[6], a daunting number of potential connections and contracts to undertake to implement a REMS solution for prescribers.

At the other end of the spectrum, there is only one major player in the e-prescription transaction space—SureScripts—which holds ~95% of that market[7]. To a company that handles the bulk of e-prescription transactions for the more than 20,000 currently marketed pharmaceutical products in the US[8], partnering to implement a unique REMS solution for pharmacies for approximately 60 products is not likely to be a business priority. The challenge is not notably easier from the pharmacy side. National retail chains represent ~21,000 stores, regional chains represent ~16,500 stores, and ~19,500 pharmacies are independent[9]. Plus, these pharmacies use a wide variety of PMSs and varying configurations of those systems.

While the challenges were many, Shepherd was successful in its quest to find a company that could implement in-workflow REMS solutions. Invaryant is a technology company that was founded on improving patients' healthcare and outcomes; as a result of their dedication to the patient, Invaryant builds solutions and networks that could address the needs of the REMS space, as well as many other challenges in our complex healthcare delivery system. Their mature platform actively serves an ever-growing network of 4,200 hospital systems, 94,000 care sites, 600,000 providers, and 191,000,000 patients. It has also passed audits by several entities, including FDA, without findings.

The most notable difference between traditional REMS systems and Invaryant's offerings is that Invaryant challenges the old adage in the REMS space that "if you've seen one REMS, you've seen one REMS." That rationale is why traditional REMS systems are a ground-up build for each and every REMS program. Invaryant's solution, by comparison, relies on a central safety center for each manufacturer that has uniquely configured solutions for each REMS program—emphasis on the word configured.

We experience software configuration all the time in our day-to-day lives, but those of us outside the world of technology rarely recognize it as such. For example, a company may configure MS Excel to build its departmental budget, store its client contact list, and model pricing for a new product. These are very different use cases, but they're all configured on the same platform, MS Excel. Invaryant takes the same approach to solutions configured on its platform. The underpinnings—security, connectivity, communication, identification (SSO), and a comprehensive network of providers—are consistent, but by virtue of configurations, they can build a REMS solution and a pharma GMP manufacturing audit solution on the same platform.

This matters more than may be obvious on the surface. For example, a manufacturer with three REMS drugs only needs to build from the ground up for one REMS on the Invaryant platform. Subsequent REMS builds leverage the existing safety system configuration and are only customized at the REMS requirement level for the program being added. This means faster, less expensive builds from the second program onward because of both programming efficiencies and the limited scope of system validation.

Beyond the initial build benefits, the Invaryant platform offers a single sign-on (SSO) solution for all REMS programs on its platform. Once you're a credentialed user on Invaryant's platform, it's simply a matter of which programs you're allowed to access by virtue of certification/enrollment. It's easier for users than having a lot of unique program-specific logins, but it gets even easier when you consider that users who have an SSO active directory never have to remember a

password specifically for REMS. They can use their network, EMR, PMS, facility login or other SSO active directory to access the Invaryant platform as a verified, known user.

While easy system access is certainly an appreciated feature, the bigger benefit is that Invaryant's SSO access can get prescribers direct access to the REMS from within their EMR, meaning that prescribers never have to leave their workflow to fulfill their REMS obligations and are therefore much more likely to fulfill those obligations on time and directly in the system, not via paper and fax. To ease completion of requirements, the HIPAA-compliant platform also prepopulates forms with information available in the EMR (e.g., lab results) or via public databases (e.g., NPI). Additionally, for prescribers who access the REMS in their EMR, notifications about those requirements are also available in the EMR, greatly increasing the likelihood that they will be seen and read.

These prescriber solutions are a win-win for prescribers and the manufacturers. Prescribers get the in-workflow solutions they want, and manufacturers in turn get lower cost of operations by virtue of reduced contact center traffic and associated staffing level decreases. Additionally, manufacturers get these in-EMR benefits without the burden of contracting with EMR providers or paying them fees for access. Invaryant's proprietary system configuration and patented Morph and Symbol technologies combine to easily connect to EMR platforms in a way that requires the EMR providers to grant access. This means that EMR access is simply a system configuration at build, not an ongoing cost of REMS operations.

While in an ideal world, all prescribers would complete their REMS requirements electronically, the reality is that some stakeholders will always use paper forms. Even when prescribers provide information to the REMS via fax, Invaryant has a solution that ingests the data contained on the fax leveraging both AI and the Invaryant patented Morph technology This benefits prescribers because, assuming forms are filled out correctly and completely, the fax data is in the REMS database within minutes of hitting send on the fax, as opposed to the 24 to 48 business hours for fax data entry by live agents for other REMS systems. Even incomplete forms move faster because the deficiencies are identified upon fax receipt, so follow-up calls happen sooner. If the information on the fax is what stands between the patient at the pharmacy and the ability to get the REMS approval for their prescription, this quick turnaround is a game-changer for patient access.

Manufacturers also benefit from Invaryant's innovations in the contact center aspects of the REMS because they reduce contact center costs, which are typically the top driver of overall operations costs for REMS programs. Invaryant's fax solution described above translates to less need for costly live agents to manually enter fax data. Their other contact center solutions can also lower operating expenses associated with live agents through use of a subject-trained, conversational, virtual contact center agent; the virtual agent can answer calls, record calls, and generate all necessary call documentation (i.e., transcription, summary call notes, and metadata keyword tags) in real time. Together, these offerings decrease the number of calls that require handling by a live agent and decrease the call handling time for both virtual and live agent calls.

Similar to prescribers, pharmacists also benefit from Invaryant's approach to REMS technology. A pharmacy chain or independent store only needs to connect its PMS to the Invaryant platform once to connect to any REMS program that operates on the Invaryant platform, and pharmacies do not have to do custom programming to connect Invaryant's bridge to their system. Invaryant's patented Morph middleware can connect to whatever type of connection the pharmacy already has for receipt of

e-prescriptions, and the necessary REMS information populates in the NCPDP SCRIPT fields already available in PMSs. The use of Morph also means that Invaryant's solution can be connected to retail, specialty, hospital, and other pharmacy types; the Invaryant system flexes to the connection needs of the pharmacy instead of requiring the pharmacy to conform with the REMS system's connection requirements.

Given the many advantages of the Invaryant system, Shepherd is excited to partner with them to bring these needed innovations to manufacturers with current or future REMS programs. Combining Invaryant's proven, innovative technology with the Shepherd team's REMS knowledge and experience means manufacturers can offer stakeholders a better REMS experience at a lower cost of ownership.

The REMS journey is far from over. Shepherd Safety Services in combination with Invaryant's Health Platform stand at the forefront of change, ready to address longstanding challenges and embrace innovative solutions. The partnership symbolizes our unwavering commitment to fostering a REMS landscape that is efficient, effective, and patient-centric. Together, we are driving the future of REMS, one seamless integration at a time.

ABOUT THE AUTHOR

Melissa Landers has more than 25 years of management consulting experience, with 20 in the biopharma industry. She focuses on regulatory strategy, program management, and large-scale program operations, with a particular focus on Risk Evaluation and Mitigation Strategies (REMS). She brings this experience to bear on products with a complex risk profile either approaching initial launch or generic competition.

Sources:

[1] Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology. 2022 Annual Report: Detecting, Assessing, Preventing, and Managing Risks. https://www.fda.gov/media/168634/download. Accessed 8/21/2023.
[2] Do the Benefits of REMS Programs Outweigh the Risks? Pharmacy Times. Nivedita Kohli. 05/19/2020.
[3] REMS Vendor Disruptions Prompt Greater US FDA Scrutiny. Pink Sheet. Brenda Sandburg. 02/24/2023.
[4] Source: Risk Evaluation and Mitigation Strategies (REMS) Integration. HL7. https://confluence.hl7.org/display/COD/Risk+Evaluation+and+Mitigation+Strategies+%28REMS%29+Integration. Accessed on 8/21/2023.
[5] From Our Perspective | Risk Evaluation and Mitigation Strategies (REMS), Part 2—Implementation: Challenges and Opportunities. FDA. https://www.fda.gov/drugs/news-events-human-drugs/our-perspective-risk-evaluation-and-mitigation-strategies-rems. Accessed 8/22/2023.
[6] EHRs Ranked by Market Share. Health Grades. Nickey Scarborough. 05/30/2023. https://www.healthgrades.com/pro/ehrs-ranked-by-market-share. Accessed 8/22/2023.
[7] Surescripts could lose market dominance under FTC agreement. Legal Dive. Robert Freedman. 08/04/2023. https://www.legaldive.com/news/surescripts-FTC-monopolistic-digital-prescription-settlement/689977. Access 8/22/2023.
[8] FDA at a Glance. FDA. 04/2023. https://www.fda.gov/about-fda/economics-staff/fda-glance. Accessed 8/22/2023.
[9] Meeting changing consumer needs: The US retail pharmacy of the future. McKinsey & Company. 03/17/2023. https://www.mckinsey.com/industries/healthcare/our-insights/meeting-changing-consumer-needs-the-us-retail-pharmacy-of-the-future. Accessed 08/22/2023.