

The state of REMS in the US

Richard Gliklich examines whether the US FDA's relatively young risk evaluation and mitigation strategies programme is working and discusses ongoing challenges.

Although it has been three years since the passage of the US Food and Drug Administration Amendments Act of 2007¹ and the risk evaluation and mitigation strategies (REMS) programme it introduced, there still exists a debate over what the clear reasons are for REMS, when the FDA should require one and how effective they have actually been in mitigating risks. The agency began approving REMS in 2008 and, as of January this year, 175 REMS had been approved.

FDAAA gave the FDA the authority to require a REMS either as a condition of approval for products with known safety risks or after approval if new safety concerns surface while the product is on the market. REMS apply to prescription drugs (new drug applications and abbreviated NDAs) and biologics (BLAs).

REMS for an NDA or BLA product must have a timetable for submission of assessments of the REMS, which includes an assessment of the REMS at 18 months, three years and at seven years. However, the FDA can require additional assessments beyond these.

The basis for requiring a REMS ostensibly stems from the risk-benefit profile of the product. If the risks outweigh the benefits, then a REMS may be necessary. When making this determination, the FDA takes into account the number of people who will likely be exposed to the medication, the seriousness of the disease or condition, the seriousness of the potential adverse events, the duration of the treatment, the expected benefits and the status of the product – ie is it a new molecular entity?

The elements of REMS include medication guides, communication plans, elements to assure safe use (ETASU) and implementation systems. Depending on the severity of the safety risks, the FDA may require only one of these elements, such as a medication guide, or a combination of these tools, with ETASUs being the most restrictive of the requirements.

A medication guide, typically a paper document that is included with a prescription medication and addresses potential adverse events and adherence issues that may affect effectiveness, is the most commonly required

element of a REMS. In addition to the medication guide, a REMS may require the inclusion of a communication plan. A communication plan targets healthcare providers by directly providing them with information on the safety concerns with the product. For example, a communication plan may specify the manufacturer distribute a letter directly to the providers with this information or utilise professional associations or societies to disseminate the information.

As mentioned above, ETASUs are the most restrictive elements that may be required of a REMS programme and are intended to address a specific serious adverse event. In order for the FDA to require an ETASU, it must determine "that the drug, which has been shown to be effective but is associated with a serious adverse drug experience, can be approved only if, or would be withdrawn unless, such elements were required; and that for a drug initially approved without ETASUs, other possible elements of a REMS are not sufficient to mitigate such serious risk"².

ETASUs fall into six categories and reflect the severity of the risk and the distribution channels that need to be made aware of those risks. These elements include:

- a special certification or training requirement. For example, a physician may need to be able to demonstrate their knowledge of the adverse events of a specific drug prior to prescribing it;
- a special certification for any entity that can dispense the medication, including physicians, pharmacists and infusion sites. This element may require that whoever dispenses the medication agrees to only do so after certain conditions are met. For example, a pharmacist may be required to verify that certain laboratory values qualify the patient for use of the drug prior to filling and dispensing the prescription;
- the medication may be dispensed only in certain settings, such as a hospital or specialty clinic;
- prior to dispensing a drug to patients, the patient must provide evidence or

documentation demonstrating that certain qualifying conditions have been met. For example, the patient may need to be counselled on the safety risks and sign a statement that he/she understands those risks;

- implementation of a monitoring system for every patient taking the medication. For example, a patient may be required to follow-up with the provider or take certain laboratory tests at certain intervals to demonstrate that he/she still meets the safe use requirements for taking the medication; and
- every patient taking the medication must be included in a registry. The data that are collected in this type of registry may include clinical outcomes, clinical and laboratory data, safety information and compliance data.

An implementation system is an element that may be required of any REMS that includes an ETASU. An implementation system is a system designed to monitor and evaluate the healthcare providers and anyone included in the distribution part of the ETASU implementation of those elements³.

Of the 175 REMS approved, 116 required only a medication guide, 37 required a medication guide and a communication plan, 21 required a combination of elements to assure safe use, a medication guide, a communication plan, and an implementation system, and one was released from the REMS requirement⁴. (See Figure 1 for approval by year.)

For those REMS requiring more than just a medication guide and a communication plan, where a complex monitoring, tracking and outcomes measurement system is needed, manufacturers may choose to implement a patient registry. A registry can assist with the tracking of the required data as well as with monitoring a required restricted-access system.

When designing a registry for a REMS requirement, researchers should consider the goals and objectives of the programme. If the primary goal is to meet a restricted distribution system requirement, also known as a performance-linked access system (PLAS), the registry is designed with the intention to collect

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data on a specific, known adverse event. With these types of programmes, all patients taking a specific product must be in the registry in order to receive access to that product.

Even if a registry is not required as part of the REMS, implementing a registry focused on safety surveillance can provide a proactive risk minimisation approach. Once a product receives approval, it typically will be prescribed to a much larger and more diverse population than was tested in the pre-approval clinical trials. Safety registries provide the opportunity to examine any unresolved safety concerns or identify and understand any risks that may not have appeared in the clinical trial stages. Furthermore, if the FDA determines a more restrictive REMS or safety monitoring system is necessary, a pre-existing safety registry may be able to provide the foundation for these programmes.

For example in 2001, Actelion's Tracleer (bosentan) was approved as an orphan drug with safety issues that required a RiskMap. Actelion was notified in early 2008 that its Tracleer RiskMap, developed in 2001, needed to meet some additional requirements for a REMS. The REMS requirement for Tracleer included a medication guide, a communication plan, ETASU and an implementation system. In this case, Actelion was already using a registry for monitoring safety signals. The company was able to use the registry data and system to address many of the surveillance requirements for the REMS.

Being prepared with a safety and risk minimisation plan and incorporating REMS development into the pre-approval phases may also help with expediting the approval process. If the FDA is unsure about accepting a product due to unknown safety risks, the development of a post-approval risk management

programme can help assuage its concerns. In one case, Xenazine (tetrabenazine), the first FDA-approved treatment for Huntington Disease⁵, attained fast-track designation, but the actual approval of the product was delayed until a REMS was developed.

Beyond evaluating the risk-benefit profile of individual products, the FDA has also implemented class-wide REMS targeted at a specific class of drug that has a high-risk profile. In February 2008, the FDA announced a REMS requirement for erythropoiesis-stimulating agents⁶, which was limited to three Amgen products. Almost immediately the provider community fired back with concerns that the REMS would be an undue burden to providers, who under the plan are required to undergo certification and training and are responsible for implementing the processes, such as ensuring all the patients are enrolled in the programme and maintaining signed acknowledgements from patients. Soon after the REMS launch in March 2010, the American Society of Clinical Oncologists sent a letter to the FDA expressing its concerns about not being included in the REMS development process and calling for the programme to use already existing physician education and training practices.

In February 2009, the FDA announced another more widespread class-targeted REMS requirement for long-acting, extended release opioid medications, affecting nearly 20 different manufacturers. Due to the overwhelming response from industry, specialty associations representing patients, providers and pharmacists, the FDA decided to postpone the REMS implementation for these medications for a year, while it gathered more feedback from stakeholders. In July 2010, two FDA advisory committees voted not to recommend the

proposed REMS because they felt the REMS should be more stringent and include not only long-acting, extended release products, but the entire class of opioid medications. The FDA is still analysing all of the feedback it has received from the committees and from public comments. Once the agency finalises its review, the FDA plans on issuing REMS requirement letters to the appropriate manufacturers⁷. In anticipation of this impending requirement and in some cases to aid in the approval of a product, some companies have voluntarily submitted a REMS. Covidien did just this with its opioid product EXALGO.

Challenges facing REMS

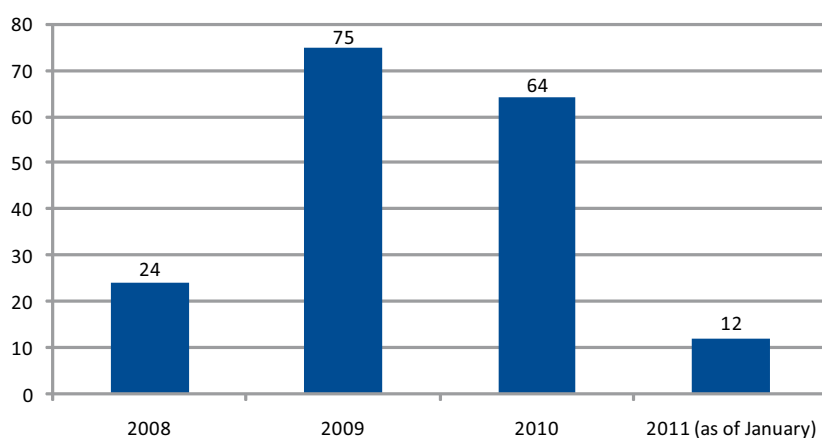
One of the concerns that arose from both of the class-wide REMS decisions was the possibility of providers not prescribing a particular drug because the ability to do so may not be worth the effort. Different organisations have proposed linking continuing education credits with the certification and training processes. For instance, at the July review meeting on the opioid REMS, the Accreditation Council for Pharmacy Education recommended that "REMS education be linked to accredited continuing pharmacy education (CPE) programs as a means of providing an incentive to pharmacists"⁸.

Encouraging the participation of providers is only one of the challenges that may affect the success of these programmes. Manufacturers need to evaluate their internal structure to determine if the organisation is operationally prepared in the event a REMS is mandated. REMS can strongly affect the market access and distribution of a product and manufacturers may incur civil penalties.

Due to the potential financial and legal impact that a REMS can have on a product, many different teams should be involved in designing the REMS strategy. A few of the teams to consider in the discussion include those of clinical research, late phase, regulatory, epidemiology, legal and brand management. Each department will be able to provide a valuable perspective to the overall goals of the programme. Manufacturers should also consider working with an experienced REMS service provider to implement the programmes, especially for those programmes that require specially designed registry and outcomes measurement tools.

Another challenge that specifically pertains to a required registry element is ensuring that the data collected is of a high quality. Although REMS are still fairly new in the overall life of risk management programmes themselves, registries have been used for monitoring risk for some time. One resource that addresses the design and implementation of high-quality safety registries, and specifically covers REMS, is the second edition of the US Agency for Healthcare

Figure 1. FDA-approved REMS



Research and Quality guide Registries for Evaluating Patient Outcomes: A User's Guide, published in September 2010. This resource provides best practices for all elements of the design and implementation of a registry and also provides case study examples⁹.

Conclusion

The young age of these programmes restricts the ability to determine just yet how successful they will be at monitoring and mitigating risks. More analysis will be possible as more REMS approach the longer assessment periods and are able to provide more data on the effectiveness of the programmes.

With that said, by establishing programmes that proactively monitor adverse events and intentionally eliminate known risks, most healthcare stakeholders agree that the ultimate goal of improving patient safety is being met. Despite many of the challenges and growing concerns from different stakeholders, the likelihood is that the number of mandated REMS will continue to

increase over time, especially as more class-wide REMS are implemented.

Pharmaceutical and biotechnology manufacturers should incorporate risk management plans early in the development process and take a proactive approach to post-approval risk management to protect and promote the success of their products.

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