Four Common Missed Opportunities When Designing and Developing a REMS Program

Debbie Cheslow, MPS
Director, Risk Management Programs, Real-World Evidence
Evidera, a PPD business

Kristin Veley, PharmD, MPH
Research Scientist and Director, REMS and Pregnancy Registries, Real-World Evidence
Evidera, a PPD business

A Risk Evaluation and Mitigation Strategy (REMS) is a complex and evolving safety program. Although the US Food and Drug Administration (FDA) ultimately determines if a REMS program is necessary, there may be more opportunities than you might realize to shape the development of your program. Proactive engagement with the FDA, for example, can make a critical difference in reducing timelines, limiting confusion, and agreeing to reasonable requirements. Here we discuss four common missed opportunities when developing a REMS program.

What Is a REMS?

The FDA requires a REMS for certain products with serious safety concerns to help ensure the benefits of the product outweigh the risks to the patient. While all FDA-approved pharmaceutical products have labeling that informs healthcare providers of the product's risks, only a small percentage require a REMS.[1] Each REMS includes safety measures unique to the safety risks associated with a particular product or class of products. The requirements may include elements to assure safe use (ETASU) or simply distribution of a medication guide or a communication plan (See Figure 1). ETASU may be required when other elements are not considered sufficient to mitigate serious risk(s). Examples of ETASU include prescriber certification, pharmacy certification, patient enrollment, evidence or documentation of safe use conditions (e.g., confirmation

Debbie Cheslow

Kristin Veley

Figure 1: Types of Risks REMS Requirements Aim to Mitigate[2]

Risk Example	Possible REMS Action
Serious Infection	Patient education on initial warning signs prior to prescribing
Severe Allergic Reaction	Healthcare provider must be certified prior to administering the product
Liver Damage	Liver function monitoring while patient is taking the drug
Severe Birth Defects	Negative pregnancy test prior to dispensing each prescription

of pregnancy testing or other monitoring results) prior to dispensing, or patient participation in a registry.

If ETASU are required as part of a REMS, a plan for implementing the ETASU will need to be developed. This plan may include a website and contact center to facilitate certification and enrollment and the creation of a database for collecting and maintaining appropriate data.

MISSED OPPORTUNITY 1
A Delayed Start

The FDA requires, reviews, and approves REMS programs, but sponsors must design and develop their own REMS programs. These programs may be large, complex, resource-intensive, and may involve multiple sponsors (e.g., in the case of a single shared REMS, a consortium of multiple companies).

Many sponsors make the mistake of only beginning development of their REMS programs when the FDA requests it. We recommend sponsors take a proactive approach, ideally starting design and development of REMS programs at least six months before submitting an application (e.g., new drug application [NDA], abbreviated new drug application [ANDA], biologics license application [BLA]). If a REMS is required, the NDA cannot be approved without final documents, including the REMS document, REMS supporting document, and REMS materials (e.g., stakeholder letters, brochures, enrollment forms).

While the FDA may release a sponsor from their commitment to have a REMS, or remove certain components of the REMS if they determine the extra measures are no longer necessary to ensure a product's benefits outweigh its risks, ETASU REMS or certain components of other REMS programs may continue to be required throughout a product's "life" on the market.

Waiting until late in the approval cycle to begin designing your REMS may put unnecessary strain on your resources and timelines, lead to rushed development of your REMS, and limit your opportunities to negotiate the specific REMS requirements with the FDA. A late start could also mean a delay in your product's approval, particularly when there are extensive FDA comments to work through in response to your submission.

But how do you know if the FDA will impose a REMS? Determining the likelihood of a REMS can be tricky. The FDA issued guidance in 2019 that outlined six factors to consider in determining the necessity of a REMS:[3]

1. The seriousness of any known or potential adverse events that may be related to the product and the background incidence of such events in the population likely to use the product
2. The expected benefit of the product with respect to the disease or condition
3. The seriousness of the disease or condition that is to be treated with the product
4. Whether the product is a new molecular entity
5. The expected or actual duration of treatment with the product
6. The estimated size of the population likely to use the product

The FDA guidance acknowledges, however, that determining the necessity of a REMS is complex and specific to the particular product.[3] Analysis of previously approved REMS programs for products in the same class (i.e., same mechanism of action) or with similar safety profiles can help provide insight into whether a REMS may be necessary for your product. For example, for each Chimeric antigen receptor (CAR) T-cell therapy approved in the US thus far, the FDA has required a REMS. Therefore, if you plan to submit an NDA/BLA for a CAR T-cell therapy, it is safe to assume a REMS will be required. Products with serious safety concerns (e.g., birth defects, life-threatening infection, or vision loss) may require more complex REMS requirements.

MISSED OPPORTUNITY 2
Failure to Proactively Engage with the FDA

If you think a REMS might be required for your product, it is advantageous to begin to strategize what you would like to propose to the FDA and engage in those discussions as early as possible. Many sponsors are hesitant to proactively contact the FDA, but, in our experience, the FDA not only encourages early outreach, they welcome the opportunity to engage in open, two-sided dialog. Proactive engagement allows you to approach the FDA with your

recommendations and gives the FDA something to react to. On the other hand, a more passive approach (i.e., waiting for the FDA to lay out what is required) may limit your ability to control the discussions.

By taking the initiative and providing your recommendations to the FDA, you may be able to speed up timelines, limit confusion, secure agreement, understand requirements, and set reasonable expectations.

MISSED OPPORTUNITY 3

Early Engagement with a Third-Party Partner

Designing and developing a REMS is a complex process involving multiple stakeholders and requiring experts in many functional areas from epidemiology, risk management, and regulatory affairs to finance, information technology, and medical writing. Strong project management is also critical for a successful REMS program.

It's important to determine whether your organization can manage those resources internally, especially if you're building your first REMS program. Not all organizations have existing staff, or the ability to hire new staff, with these skillsets. You will need to assess the capabilities and availabilities of resources from several functional areas and determine whether they have specific experience with REMS, not just in their respective areas of expertise. Also, you may not need full time staff if you only have one or two products with REMS programs in your company.

Alignment of REMS resources is also critical. Internal departments may have different agendas and decision-making processes. It's important to establish and align the various goals across the organization. A third-party vendor can help streamline that process by creating and managing one governance committee that can help bring your organization into alignment. Additionally, if you are a member of a single shared REMS, a Project Management Office vendor is critical to objectively manage complex logistics, finances, and meetings; guide consensus planning; and oversee voting and decision making. Outsourcing functions can give you the expertise you need when you need it.

MISSED OPPORTUNITY 4

Not Negotiating with the FDA

Once the FDA determines a REMS is necessary for a product, manufacturers must design their specific REMS. While the need for a REMS is rarely up for negotiation, the scope of what the REMS includes is something you may be able to influence if you have a strong rationale; after all, the FDA does not want to create undue barriers to access or burden patients, caregivers, or the healthcare delivery system with the REMS requirements. In our experience, the FDA has been open to these discussions, which can lead to decreased burden on stakeholders as well as sponsors. Negotiations may continue after submission of the application (e.g., NDA, ANDA, BLA) and REMS documents.

Early and ongoing negotiations with the FDA may not only inform your activity during the very limited implementation window, they may give you a stronger voice in how the details of your implementation are built out, help you avoid a delayed launch if you encounter implementation issues, or handle unexpected feedback from the FDA. During this time, comments and revisions from the FDA should be incorporated into REMS documents while you are building your infrastructure (i.e., contact center, database, and website) and processes so that you are ready to go live once approval is received.

A clear plan for assessing the REMS must be established as part of REMS design and development of the REMS submission documents. After implementation, ongoing assessments evaluate the effectiveness of the REMS. These assessments have tight timelines for submission (i.e., 60 days from data cut-off to report submission), so it is essential to thoroughly understand the metrics you have committed to reporting. Early conversations with the FDA can, once again, help you avoid unwanted surprises and potentially influence the reporting process.

Conclusion

While the elements of a REMS program are mandated by the FDA, there are ways you can influence not just the approval timeline but the scope of the REMS. Early and ongoing engagement, using a third-party to manage the process, and negotiating with the FDA can help limit confusion, clarify expectations, and build consensus on reasonable requirements. This, in turn, will decrease the burden on you, the sponsor, as well as, the burden on patients, caregivers, and the healthcare delivery system. ■

For more information, please contact Debbie.Cheslow@ppd.com or Kristin.Veley@evidera.com.

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