

FDA Draft REMS Guidance: Implications and Opportunities for REMS Lifecycle Management

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History of Drug Safety Initiatives

Nearly 200 years ago in 1820, the US Pharmacopoeia was created to define what a drug was and develop a system of standards for uniformity in composition, purity, and strength. Although a simplistic approach to drug safety for its time, this development pioneered the way for the passage of the Pure Food and Drug Acts of 1906. One key component of this law included provisions against “misbranding” – if a drug contained morphine, cocaine, opiates, or any other dangerous or habit-forming drug and its label did not adequately identify the proportion or quantity, the drug-manufacturer was in violation of the law. Now over 100 years old, this act’s importance to modern-day drug safety is threefold: first, it represents one of the first major consumer protection laws in US history. Second, the Bureau of Chemistry, who had oversight responsibility for the act, became the predecessor of the Food and Drug Administration. Finally, the act provided a foundation for government and industry to work collaboratively to improve drug manufacturing practices. From the early days of drug safety to the evolution of today’s REMS, drug safety continues to progress, present challenges, and opportunities for advancement. This evolution and implications for future drug safety are explored throughout this paper.

In 1912, the Sherley Amendment was enacted to prohibit false claims on labels – Mrs. Winslow’s Soothing Syrup was used to soothe colicky and teething babies, but contained (unlabeled) morphine, killing many babies. By 1927, the Bureau of Chemistry was reorganized and by 1930, the agency was officially named the Food and Drug Administration. In 1937, a significant event that shaped the future of drug introduction into the market was the Elixir of Sulfanilamide tragedy. The drug contained a solvent that was neither tested in a laboratory nor questioned by the medical literature which proved to be fatal. The solvent, today’s anti-freeze, resulted in the death of 107 people, mostly children. In response, Congress passed the Food, Drug, and Cosmetic Act of 1938. In addition to extending oversight to medical devices and cosmetics, this act required that new drugs: had to undergo safety testing, be approved by the FDA prior to marketing, and had adequate directions for safe use.

In the late 1950s, Thalidomide was introduced in Europe to alleviate the symptoms of morning sickness for pregnant women. The drug was used in 46 countries, aside from the US, and it became clear by the early 1960s that Thalidomide was causing stillbirths and serious birth defects. Due to the media exposure of these events around the world, public outcry was at a fever pitch and demanded stronger US government action. As a result, drug manufacturers were now required to conduct both safety and efficacy testing. Additionally, the FDA had to approve drug advertising, labeling, and human trials prior to release to market.

During the latter part of the twentieth century, drug safety evolved as the industry began shifting from a reactive to a proactive risk management response. In the late 1970s, patient package inserts (PPI) were introduced for oral contraceptives and there was a rise in the use of “Dear Healthcare Provider” letters. In 1982, Accutane was approved and the initial risk management was limited to labeling, describing the risk of teratogenicity in the Contraindications, Warnings and Precautions sections of the package insert and in a patient information brochure. As additional risks came to light, several other interventions were subsequently added to the risk management program, including a pregnancy prevention program (PPP). Many of the elements included in the Accutane program, and others like it, are still being used in REMS (Risk Evaluation and Mitigation Strategy) and RMPs (Risk Management Programs) today.

After the turn of the century, several products, including Rezulin and VIOXX, were removed from the market due to safety concerns and the FDA responded by releasing guidance on Premarketing Risk Assessment, Development and Use of Risk Minimization Action Plans (RiskMAP), and Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. Together, these documents described the FDA's concept of safety monitoring and gave manufacturers direction for tools and interventions to implement in order to mitigate risk and ensure adherence to product labeling. Unless it was accompanied by a RiskMAP, the FDA would not consider approving a product. Examples of products with RiskMAPs include: Accutane, Clozapine, and Thalidomide. These risk management programs include: medication guides, prescriber certification, and patient enrollment in an access registry.

Recent Experiences - REMS After 2 Years

In September 2006, the Institute of Medicine (IOM) of the National Academies released the report, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. This report detailed deficiencies with post-marketing drug safety and dangers to the public. Coupled with the VIOXX withdrawal from market in 2004 and increased media and congressional scrutiny, the Food and Drug Administration Amendments Act (FDAAA) was signed into law in September 2007 to mitigate these concerns and protect the public health. This law granted the FDA with the authority to:

- Require post-approval studies or clinical trials to assess a known or serious risk, or to learn more about a hypothetical serious risk;
- Require that new safety information be added to the product labeling; and
- Require that companies submit Risk Evaluation and Mitigation Strategies (REMS) when deemed necessary to ensure that the product's benefits outweigh the risks.

As the industry has continued to evolve from RiskMAPs to REMS, 16 of the previous RiskMAP programs went on to become REMS; one-third of new chemical entities approved over the last two years have had REMS associated with them—the vast majority of those have been medication guides, and only a minority have included more restrictive interventions, such as prescriber certification or patient enrollment in a registry.

In the two years since the FDAAA became law, there have been many ripple effects in the industry. First, Rimonabant, a drug that showed promise for the treatment of obesity, was not approved by the FDA due to safety concerns associated with risk of psychiatric events. Other manufacturers abandoned their development of similar drugs when Phase III data indicated higher risks associated with higher doses. Conversely, new products have been approved that had previously “stalled” in the approval process. Yet, the FDA approved these products with the comfort that they were accompanied by comprehensive REMS programs.

Other emerging trends that have appeared since REMS has come into existence include a harmonization of programs for “like” products, early communications about risks, and increased scrutiny for REMS assessments. For example, the FDA simultaneously reviewed REMS programs for two similar products from different manufacturers: NPlate NEXUS and Promacta CARES. Both drugs are used to treat chronic ITP (idiopathic thrombocytopenic purpura) and have similar REMS, including restricted distribution and prescriber certification. During its review, the FDA attempted to harmonize the tools and forms used for these different programs. Following suit, the FDA has implemented class REMS for quinolones, Tumor Necrosis Factor (TNF) blockers, erythropoietin stimulating agents, and anti-epileptics. The FDA has also been pushing for a class REMS for long-acting opioids.

Additionally, the FDA has become more proactive in communicating about potential safety risks by reaching out to the healthcare and patient community through podcasts, newsletters, and web updates. They have also been asking manufacturers to use professional societies as dissemination

channels for risk communications and have been requesting that sponsors conduct risk-only advertising in major medical journals. Finally, the FDA has become much more preemptive in communicating about ongoing safety reviews and possible risk mitigation strategies. As the FDA has become more sophisticated in its approach to REMS, it is also requiring more stringent standards related to REMS assessments.

However, while the FDA has become increasingly more erudite regarding REMS, inconsistencies still exist. First, the FDA has been extending its REMS authority beyond safety risks and requiring REMS for products that show a relative lack of efficacy. Similarly, they have been urging REMS for mitigation of off-label product use. Second, in some circumstances, the FDA has been advocating for less intensive REMS. For example, they proposed an “interim” REMS solution that was less restrictive and intensive while determining a longer-term strategy for the opioid-class REMS. They have also been attempting to convince Advisory Committees to negotiate for less restrictive REMS that have been proposed by sponsors. Finally, the FDA has been sending mixed messages to sponsors by removing and then re-inserting REMS elements into the final REMS program immediately prior to the PDUFA (Prescription Drug User Fee Act) reauthorization date, and in some cases, have missed the PDUFA dates altogether. The FDA has also promoted and then delayed the opioid class REMS, extending deadlines to seek public comment.

These inconsistencies have resulted in confusion among manufacturers and have undermined their ability to develop sound strategies for building effective REMS. Some companies have proposed a medication guide only as a REMS program, which did not fulfill the FDA’s expectation of communicating risk to patients. Others have offered “lighter” strategies, such as patient package inserts, to which the FDA responded harshly, requiring these companies to develop very restrictive REMS programs. In some instances, companies proposed Voluntary Elements to Assure Safe Use and the FDA then required a full-fledged REMS. Finally, in many cases, the FDA has been re-negotiating REMS with companies after Advisory Committee meetings. In response to these many confusing aspects of the FDAAA, the Draft REMS Guidance was issued in September 2009.

Draft REMS Guidance - Observations and Implications

The Draft REMS Guidance has offered several key insights for directing companies in their development of REMS. However, the Guidance also has left some areas up for interpretation, thus providing an opportunity for the industry to define the standards and science behind managing risk.

The Background section of the document proposes the following key elements:

1. Companies may voluntarily submit a REMS if FDA determines that a REMS is not required or may undertake voluntary risk mitigation measures outside of a REMS
2. Companies may voluntarily:
 - a. conduct more frequent assessments than required
 - b. modify the assessment plan and/or the elements of the REMS based upon results of assessments; and
 - c. modify the REMS goal.

The Guidance also describes REMS in relation to RiskMAPs. As stated by the FDA, “many of the principles that were included in the RiskMAP guidance are embodied in the FDAAA REMS provisions.” One observation is that similar to the RiskMAP guidance, the FDA primarily focuses on the Medication Guide as the main communication vehicle for patients. This represents an opportunity as there is no further discussion about other educational strategies for patients. The communications plan and Elements to Assure Safe Use are also similar to those described in the RiskMAP guidance.

A timetable for assessments is also established in the Guidance document and the schedule requires assessments at the 18, 36, and 84-month marks for New Drug Applications (NDAs). A timetable for assessments is not required for Abbreviated New Drug Applications (ANDAs). As indicated previously, the timetable may be modified after the 36-month mark if the assessments identify risks and show that they are being adequately managed. Experience-to-date shows that the FDA is requesting more frequent assessments than the minimum requirement.

The REMS Supporting Document section provides direction on developing a rationale and supporting information for a REMS program. Specifically, it advises that the following be included in the REMS:

Background Section – This section should include a rationale for why a REMS is required and a summary of how the proposed strategies will mitigate risks. Additionally, a description of any safety information that makes a REMS necessary should be included. The background section should also cover:

- Risk characterization – this describes the severity, magnitude and frequency of the risk and should include discussion about incidence and populations at risk.
- Regulatory precedents – the sponsor should discuss previous experience by other companies or organizations in managing risks associated with similar products and the success of these efforts.
- Other supportive evidence – this describes any evidence that tools proposed in the REMS have been shown to be effective in mitigating or managing risks.

Goals - There should be one overall REMS goal, as well as individual goals for each element of the REMS addressing how each assures safe use.

Supporting Information About Each Proposed Element - In this section, each tool proposed in the REMS described should have a comprehensive description, including how and why it was chosen and specifically how it will mitigate risks. Secondly, this section introduces the concept of pre-testing by recommending that evidence of the effectiveness of tools be submitted with the REMS. Additionally, it is suggested that patients or other stakeholders provide input regarding the feasibility of the REMS.

REMS Assessment Plan - This section should describe the plan to assess the REMS elements and evaluate the extent to which each of the elements is meeting its intended goals and the need for modification. Specifically, this section should address:

- Evaluation methods for the REMS and each of its elements,
- Targeted values for each measure and the timeframe for achieving them,
- A description of what would trigger a REMS modification,
- Types of data to be collected,
- Plans to assess unintended or unfavorable consequences after implementation, and
- Any post-approval or clinical trial information to investigate a safety issue.
- Survey instruments should also be included in the REMS supporting document.

If a medication guide is proposed:

- a survey should be included that evaluates patient understanding,
- a report should be provided on periodic assessment of distribution and dispensing, and
- a report should be provided on non-adherence and any corrective actions taken.

Other Relevant Information Section - This section requests information about who in the company is responsible for REMS policy, implementation, and management. This section also requests organizational charts showing where in the company the risk management department resides.

REMS Modification - A new section in the Guidance document focuses on the lifecycle of REMS management. Many REMS programs that were implemented 18 months to two years ago are now in the process of submitting assessments. These assessments will inform decisions regarding program modification to achieve intended goals. The Guidance document states that companies must submit their assessments according to the agreed-upon timetable. However, additional assessments can be submitted at any time. If those assessments suggest that the REMS is performing at or better than expected, there is the additional opportunity to propose modification to the REMS program. A modification may only be proposed in conjunction with an assessment. Proposed modifications may include:

- an enhancement or reduction to the REMS,
- addition, modification, or removal of a REMS element,
- additions or modifications to the assessment timetable, and
- a proposal to eliminate assessments after the 36-month mark.

Each REMS modification submission must include the previously approved REMS with all changes highlighted. Additionally, a rationale and description of proposed modifications and impact on other REMS elements must also be included.

Interpreting the Guidance

While much of the language is very similar to what was in the RiskMAP guidance document, there are some favorable twists from the Draft Guidance. The voluntary elements of the guidance indicate an opportunity for companies to negotiate what is ultimately included in the REMS program. In some cases, companies that have committed to providing additional interventions have actually been required to do less. Additional opportunities exist as the FDA begins to address REMS lifecycle management and the ability to shorten terms of assessments and modify REMS elements or goals.

Although the Draft Guidance provided clarification on the practicalities of developing and submitting a REMS, some missing pieces are still evident and may prove to be challenging for companies to address. First, many companies have typically dealt with REMS in a dispersed approach across therapeutic teams. Now, companies will have to think more strategically about developing a centralized approach to REMS. In some companies, having a centralized strategy for REMS management reflects a dramatic shift in management. Some have dealt with this transition by using external vendors, while others have been able to reorganize to create a centrally coordinated role for REMS management that includes key stakeholders throughout the company.

Second, the document lacks guidance for taking an evidence-based approach to risk characterization and REMS program design. In a case study performed by ParagonRx, a manufacturer identified 30 potential tools it would include in a risk management strategy during a brainstorming session. ParagonRx conducted a Failure Mode and Effects Analysis (FMEA) on each tool to evaluate its effectiveness. Results of this analysis showed that nearly 50% were not needed for the program – 14 of the tools were found to be irrelevant and had they been implemented, potentially wasteful. 12 additional tools, not identified during the brainstorming process, were ultimately implemented. The old and new tools were consolidated into 18 tools that provided outreach to physicians, nurses, patients, and pharmacists. Without identifying a validated approach to the development of REMS programs, there is risk of interpretation, gaps in identifying needed tools, and potential waste. Other risk-intensive industries use evidence-based methodologies, such as FMEA, that could be applied to the pharmaceutical industry.

A third missing piece in the document is support for how to strike a balance between achieving risk mitigation and continuing to enable access to a product. An additional study conducted by ParagonRx evaluated physician intent to prescribe a drug with varying intensity of risk management strategies. The study showed that with an onerous and restrictive set of risk management interventions, intent to prescribe could decrease as much as 58% from baseline. However, the study also showed that if given the appropriate set of tools, it could actually increase a physician's willingness to prescribe. The right tools can help them overcome their reluctance to prescribe a drug with a risk, instill more confidence in prescribing, and allow for more product prescriptions than they might have had in the absence of risk mitigation tools. The increase in intent to prescribe can be as high as 40% – 50%.

An additional gap in the REMS Guidance Document is the lack of introduction of new tools or systems to assist in risk mitigation. A number of other risk-intensive industries, including aerospace, aviation, and nuclear have developed innovations and tools that could be adapted and incorporated into pharmaceutical risk management programs. A simple checklist, as demonstrated by Dr. Peter Pronovost's success in reducing central line infections in the ICU, could provide easy reminders to physicians about the steps they need to take prior to prescribing a drug. Safety checklists are also used in the aviation industry.

REMS Lifecycle Management

The draft guidance seems to indicate that the industry should be gearing up for REMS lifecycle management – that is management of the program over a continuum. There are three phases to this lifecycle that have become evident: 1.) design of the original REMS program, 2.) active implementation and management of the REMS, and 3.) anticipating and implementing modifications to the REMS.

- 1.) As indicated previously, companies should look to other industries to develop validated approaches for designing risk mitigation strategies. There may be resources in physicians who are already managing products with similar risks, and who have innovated techniques, procedures, methods, and knowledge in their practice that could be incorporated into the design of REMS tools. Additionally, companies need to continue to be cognizant of the balance between managing risks and increasing prescriber confidence.
- 2.) Companies need to begin to organize in such a way to actively manage and implement REMS programs, centrally coordinating internal departments and external vendors to make sure that all elements of REMS are implemented and monitored; making sure that risk management processes and procedures are reflected in the standard operating procedures of other functions within a company so that conflicts and delays are not encountered; and use project tracking and management systems to monitor interim measures of program implementation
- 3.) Prior to REMS implementation and built into its design, companies should anticipate modifications to REMS programs. They should also be prepared to conduct interim and earlier assessments of surrogate measures of effectiveness; modifying both the REMS and the non-REMS tools toward the goal of continuously improving the program and achieving the ultimate REMS goals.

A practical example of REMS lifecycle management would incorporate detailed metrics, including the required 18, 36, and 84-month assessments, but also interim measures such as:

- % reach to audience vs. goal
- % web hits/material downloads vs. expected
- % ad placements vs. goal
- % med guide disseminated vs. goal
- % awareness of risk messages

If tracked over time or benchmarked against regions, these measures could provide companies with the opportunity to take corrective actions well in advance of the initial performance report to the FDA. These data could also inform decisions about making proposed modifications to REMS programs.

In response to the Draft Guidance, there will be a number of interesting developments to follow in the coming months. First, the industry will be crafting their responses to the document and lobbying for what are reasonable expectations and recommendations. Second, the first REMS assessments will be due shortly and while they may not be published, they will likely influence the FDA to make additional requests and requirements based on their findings. Third, companies will begin to organize themselves in order to prepare for the final guidance document when it is released. They will be evaluating their organizational structures, their ability to monitor REMS-associated data, and adapt to a REMS lifecycle management approach.

Moving Forward to Building a Future Science

It seems unlikely that upon release of the final REMS guidance, the current pharmaceutical risk management practices will make the giant leap necessary to become a credible scientific discipline. However, if companies can ask the right questions and apply knowledge learned from other industries, they can collectively begin taking steps to participate in the emergence of a new science of pharmaceutical risk management. Some considerations for propelling this movement forward:

- What are the scientific principles behind pharmaceutical risk management?
- Are there benchmarks or principles from other industries that could be adopted or applied to this science?
- What sources of information does the industry have about REMS and findings from REMS programs?
- Does the industry need a new risk management publication? What rigors are in place with which to review these publications?
- Can REMS assessment data be anonymized so that it can be shared among the industry?

Conclusions

While the progress made between enactment of the FDAAA in 2007 and the issuance of the REMS Draft Guidance in 2009 seems incremental, this chapter in the long history of drug safety since the legislative acts of the early 1900s is far from over. The industry still has much to learn from its colleagues in other risk-intensive industries. As the FDA continues to work out the kinks related to REMS, it will hopefully be able to provide more consistent guidance and clearer messages. On the other hand, there are a number of opportunities for the industry to pave the way related to voluntary elements, conducting earlier and more frequent assessments, and modifying REMS programs. The key to success in managing REMS going forward will be preparation. Companies must be prepared to design, implement, monitor, and manage the lifecycle of REMS programs. Additionally, open lines of communication with the FDA throughout the REMS development phase are critical to reducing uncertainty. Designing and implementing thorough assessment plans will also be key to ensuring that companies are able to navigate the REMS waters. Early and frequent assessment of interim measures, as well as required measures, can provide important information about the effectiveness of REMS elements and whether modifications are needed. Finally, the pharmaceutical industry needs to be proactive in its advocacy for making pharmaceutical risk management a credible scientific discipline. There is momentum and opportunity to turn the recent safety events and subsequent legislation into a pivotal moment in the history of drug safety in the US.