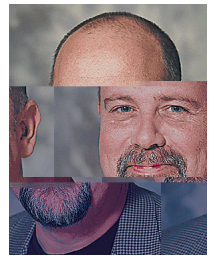
As REMS Requirements Simplify, Participants Need To Catch Up

BY JOHN CARROLL

For more than three years, regulators at the U.S. Food and Drug Administration worked to hammer out a common risk evaluation and mitigation strategy (REMS) program for extended-release and long-acting opioids. These pain medications have a long history of abuse and each has had a REMS of its own. Now, with the FDA's release of a comprehensive REMS program in July, 20 manufacturers have a common approach to education support for physicians who prescribe these drugs.



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The umbrella REMS program for pain therapies fits neatly into the FDA's revised approach to safety requirements with an eye to simplifying the rules of the game — this is important as new complex biologics hitting the market qualify for detailed REMS programs.

Congress established the REMS requirement in 2007 when drug-related safety issues prompted legislators to mandate that the FDA require a REMS every time a manufacturer needed to go beyond labeling requirements to help healthcare professionals and patients manage potential serious risks. Some product-specific REMSs were simple. Others came with a host of steps that challenged even the best compliance efforts of physicians and patients.

Under the new REMS program requirements, the FDA may simply want a medication guide added to the prescribing information to help patients understand how the drug works, how to take the drug, and what the side effects could be. More complex medications will require a program in which conditions of safe use must be tracked (e.g., blood levels or pregnancy test results), and product distribution tied to those conditions. To evaluate whether a REMS is achieving its intended goals will require assessments that involve surveying stakeholders and tracking communications outreach and other metrics specific to the design and goals of the REMS program.

For example, when phentermine-topiramate (Qsymia) was approved — the first new weight-loss drug in more than a decade — the FDA spelled out an exacting REMS. The drug is available only through certified mail order pharmacies, which are required to hand out detailed medication guides that highlight risks. The drug is linked to deformities in newborns, so doctors who prescribe it to women of childbearing age must have a negative pregnancy test in hand before they prescribe the first dose. And physicians are given careful instructions on how to counsel patients.

Changing with experience

"REMS programs are evolving as a result of experience," says Frank Gallo, executive director of risk management for Wilmington, N.C.-based PPD, a contract research organization. Gallo should know — he was involved in drug safety programs that preceded the REMS initiative. Gallo has covered everything from risk management services to communications plans — all intended to ensure the safe use of products under development by manufacturers that work with PPD.

"Since 2011, the FDA has exempted more than 120 products from their REMS programs," says Gallo. "Where there is a heavy burden on doctors, pharmacists, and patients, the FDA is working to reduce those programs."

When considering the consolidation of multiple programs into a single REMS program, the FDA starts by requesting that the companies involved put together a single program. Those companies then may create a consortium and set up committees to hammer out operations, legal aspects, and more. This happened in 2004 with oral acne medications, and in 2008, the FDA deemed the results to be "in effect" a REMS program.

"There were four products with nearly identical risk management programs," says Gallo. "It was less burdensome to have doctors, patients, and pharmacists register for a single program rather than separately." If stakeholders are using multiple products in the same class, he says, "they prefer when possible to sign up for a single program to prescribe, dispense, and use that class of medication."

"Some of the FDA press releases and white papers show that the number of REMS programs has been decreasing," says Dat Nguyen, PharmD, scientific affairs director

for the late-phase services group at PRA, a Raleigh, N.C.-based contract research organization. "They're releasing [drug] sponsors from their obligations and not requiring as much. "I think they're beginning to see, based on some of the data they have collected, that some of these programs may or may not be meeting their intended goals," Nguyen says. Some of these REMS programs have an assessment requirement where the sponsors must determine whether their REMS programs are meeting their goals, he explains. However, without a baseline comparator, says Nguyen, it is difficult for the manufacturer and the FDA to assess whether the program is having an impact.

Regulators are also getting better at choosing where they want to make a stand. "They're becoming more focused in evaluating the risk," says Nguyen. The FDA will consider, for example, whether a product or a class of drugs poses a significant population-based risk. "Initial REMS efforts cast a very broad net. Now, FDA officials are "more cognizant of the mandate they're imposing and reevaluating which drugs need it."

REMS for biologics

For injectables and the newer biologics on the market, it's fairly straightforward, says Nguyen. Before physicians can prescribe a drug handled by a specialty pharmacy, they have to complete the education requirement outlined in the REMS program. "It seems biologics have more REMS programs," says Nguyen. "It's all about the risk associated with the drug." That makes sense, he adds. "Large-molecule drugs are more complex treatments often associated with a host of potential serious side effects."

Gallo agrees that when new drugs make it to market, the FDA may require more complex REMS programs to ensure that the program design is commensurate with the risks. But when, for example, the only requirement is for a medication guide to be dispensed with each prescription, increasingly the agency is dropping the formal REMS program requirement.

"The FDA has done a very good job of ensuring that companies that have REMS obligations are meeting them and at the same time listening to stakeholders to improve programs," says Gallo.

Adapting with technology

New technologies have improved the exchange of data, but not everyone is satisfied.

"I think there's a stated desire by the FDA — and, frankly, by physicians and pharmacies — that REMS programs be more integrated into existing technical processes," says Doug Lawrence, vice president of REMS at McKesson Specialty Health. "The short answer is we'll see more of these activities embedded into work processes to minimize disruption to stakeholders."

Gallo agrees. "It's critical for REMS programs to adapt to evolving technology. If you think of a REMS, it's set up for known risks and to assure an appropriate risk-to-benefit ratio. It has to work in current business practices. As practices evolve, REMS programs have to evolve, from manual to automated authorization."

For now, many physicians and pharmacies continue to lag in adopting cutting-edge technologies, so regulatory flexibility is required — and probably will be for years to come.

"We don't know if in five years there will be 100 percent use of electronic medical records or 70 percent," notes Gallo. "For REMS programs, we have to satisfy multiple modalities. For example, for surveys, you can contact a call center, download a survey online, or mail it as a hard copy.

"We partnered with Microsoft on the first REMS-specific technology platform," says Gallo. "We can build it all on the same platform, working with one sponsor or a number of sponsors. All will have the same access in real time."

Managing and tracking requires being able to digest different data from different places, Gallo adds. "This technology platform approach provides a real-time view across the board instead of grabbing snapshots in time from disparate places. If you're a pharma company, the regulatory group has to manage the regulatory documents; the commercial group will likely manage the communication components and call center; and the epidemiology team will manage assessments and surveys. These different pieces must be managed as a single program."

In part, the FDA's acceptance of class-based REMS programs stems from a recognition of the burden they can impose on a drug manufacturer.

Technology will bring it all together. The FDA is willing to partner with all involved to build on a growing knowledge base and to do the best job possible implementing REMS programs.

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