BY ROBIN ROBINSON

POSTLAUNCH: A REMS Focus

REMS, adverse events, postmarketing research, and patient recruitment are just a few of the challenges drug sponsors face in this late-stage phase.

DR. CYNTHIA VERST ■ *i3 Innovus*

"One of the key challenges in conducting postmarketing research is ensuring the successful trial participation of community-based practitioners."

According to industry experts, the impact of the updated REMS policy in 2007 has had limited impact on the industry thus far.

The FDA was granted expanded authority to require REMS (risk evaluation and mitigation strategies) for new drug applications or for existing drugs where the FDA has determined that REMS are necessary to ensure that the benefits of a drug outweigh the risks.

REMS should include specific, measureable goals to demonstrate particular health outcomes or knowledge related to risk, our experts say. Additionally, REMS may include a communication plan targeted at healthcare providers and medication guides for patients. Periodic assessments of the targeted audiences — healthcare providers, pharmacists, and patients — are required to monitor the effectiveness of REMS programs. The process of designing and implementing REMS requires drugmakers to rethink all aspects of postmarketing activities, and this can be a new positive step toward better communication and health outcomes, our experts say.

Postlaunch: The Impact of REMS

According to Darshan Kulkarni, Pharm.D., Esq., principal attorney at Kulkarni, the impact of the Food and Drug Administration Amendments Act (FDAAA), which granted the FDA expanded authority to require REMS, so far has been limited.

"Of the 14 REMS that have been approved, only two of them have required a more involved plan of action, including the use of communication plans," Dr. Kulkarni says. "REMS seem to be placing additional burdens on the FDA and requiring further allocation of the FDA's already limited resources. While it is difficult at present to estimate the future impact that the reallocation of the FDA's resources will finally have on marketed products, it is safe to say FDAAA and REMS will foster an environment that will allow for greater collaboration between healthcare providers and pharmaceutical companies and will help address several concerns regarding drug safety."

According to David Selkirk, senior director at Clinimetrics, REMS are having a large impact on late-phase research and logistics.

"Distribution logistics and product access can be significantly affected," Mr. Selkirk says. "Budgeting considerations also come into play. If the cost of a REMS is significant, the price point for the product launch may be influenced by that."

Consequently, sponsor companies will be reviewing their early-phase data with a great deal of scrutiny knowing the requirements that could come into play further down the development road, he says.

According to Dr. Kulkarni, 12 of the 14 REMS approved to date were only medication guides.

This extreme focus on medication guides can cause some negative ramifications on the consumer end, says Doreen Moran, senior digital strategist at Sudler Digital.

"REMS requirements are forcing product managers to 'oversell' medication guides on their Web sites," she says. "Web site best practices for content focus on chunking information, but a medication guide is usually 10-plus pages of dense information in a PDF. I've seen product sites where there are three med guide links and a navigation tab. That's just overkill. Worse, it creates a bad user experience, so as the industry is trying to protect itself; it can actually be detrimental to consumers who are looking to gather the best information about a product."

"When REMS elements are designed and implemented effectively, they can be valuable tools for marketing a product," says Kathy

FAST FACT

THE WORLD PHARMACOVIGILANCE MARKET WAS VALUED AT AROUND $1.86 BILLION IN 2007 AND IS EXPECTED TO REACH $2.25 BILLION IN 2015.

Source: Frost & Sullivan

MICHAEL PARISI ■ *Altum, part of CommonHealth*

"Marketing a product within a REMS environment requires careful thought and attention to the communication surrounding a brand, as many parties are involved with patients and their care."

Bronshtein, senior VP, chief compliance officer, at Sudler & Hennessey. "With the new FDA leadership, REMS appear to be here to stay. Companies need to embrace REMS, optimize the value of the REMS tactical elements, and put them to work for their brands."

Developing effective REMS requires a plan that provides thorough targeted education requirements for healthcare professionals and enhances confidence in product utilization, Ms. Bronshtein adds.

"An effective REMS program will support patient awareness of the risks and benefits of the therapeutic regimen, as well as patient compliance and persistence of therapy," she says. "A solid REMS quickly identifies, through regular assessments and reporting, any anomalies with product performance, patient reactions, and outcomes and results in educated prescribers and consumers."

Postlaunch: Adverse Events

Adverse event reporting is never far from the minds of marketers postlaunch, especially now with the advent of social media and online interaction with consumers.

In November 2009, the FDA held a public two-day hearing to discuss the promotion of FDA-regulated medical products using the Internet and social media tools. AE reporting was a major focal point of the agenda, and many speakers, including legal counsel from PhRMA, noted that online adverse event reporting should be held to the same criteria required of other media and that the industry's trepidation and the FDA's scrutiny of AEs online is unfounded.

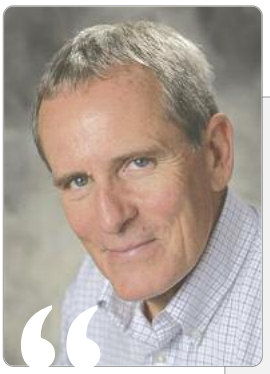
"As multiple presentations in the FDA social media hearings laid out, the industry's fear of online AE conversations is highly exaggerated in comparison with the actual reporting of AEs online," says R. Shane Kennedy, executive VP, managing director, at Sudler Digital. "According to Nielsen BuzzMetrics, there is a 0.2% rate for reportable events."

Being active and responsive online is the best option for building relationships with consumers, he says, especially since it is more common for consumers to report adverse events than for physicians to report them.

"The industry needs to listen to these conversations and respond to them when appropriate," Mr. Kennedy says. "The conversations will take place with or without you, and adverse events will take place with or without you."

Monitors are still the best resource — either via an in-person site visit or remote monitoring — to ensure that safety information is appropriately obtained and collected.

This heightened postmarketing surveillance helps to keep the safety profile of marketed therapies as current as possible, Mr. Selkirk of Clinimetrics says.



JOHN HALL ■ *Quintiles*

To truly create a system promoting safety, there needs be a proactive approach both before and after medicines are launched."

"When late-phase trials are undertaken, adverse events are generally proactively solicited from patients and thus systematically collected for analysis," he says. "Due to limited healthcare resources, it is widely believed that the number of these occurrences that are actually reported postlaunch is very low."

Manufacturers have traditionally regarded drug safety as a proactive process for medicines in clinical development, but a reactive process for medicines already on the market, says John Hall, global medical affairs, epidemiology and outcomes research, at Quintiles.

"All of the stakeholders should be encouraged to proactively evaluate, determine, and define their roles in drug safety," he says. "To truly create a system promoting safety, there needs be a proactive approach both before and after medicines are launched. Likewise, action from other stakeholders, including payers, providers, and the media, must change to include the voice of the patient regarding systematic drug safety reform."

While there is tremendous pressure on the FDA and global regulatory bodies to accelerate the approval of products that demonstrate "real" clinical benefits, there is also a heightened sense of caution due to the lack of long-term safety data, especially with biologic drugs that may have very different profiles than traditional small molecules.

"Marketing a product within a REMS environment requires careful thought and attention to the communication surrounding a brand and the risk associated with its use, as many parties — professional and consumer — are involved with patients and their care," says Michael Parisi, president of Altum, part of CommonHealth.

Postlaunch: Phase IV Activities

One of the best practices for Phase IV and postlaunch activities is to simplify the approach, Mr. Selkirk says.

"Sponsor organizations often have large clinical research departments that are accustomed to conducting very complex global studies," he says. "It is important to remember that the efficacy and safety profiles of the product in humans has already been statistically proven in

PHARMACOVIGILANCE MARKET

The challenge of managing adverse events in an optimal and efficient way and, at the same time, adhering to regulatory requirements has dictated the need for cutting-edge pharmacovigilance tools and technologies.

Regulatory bodies such as the FDA and EMEA are intensifying safety regulations, thereby boosting the adoption rates of pharmacovigilance systems by pharmaceutical companies. The need to operate in a cost-effective way is inducing pharmaceutical companies to outsource/offshore their pharmacovigilance operations.

For large companies, the volume of adverse events is sizeable. Even a product from a midsize company can generate a high volume of adverse events. There is significant potential for outsourcing/offhsoring for midsized companies as well.

Most top pharmaceutical companies have well-established systems and processes. Consequently, they are not willing to replace these systems as this entails high costs and is also time-consuming.

Moreover, the migration of data from one system to another tends to be expensive for most companies. Aligning existing processes to fit in the new system is difficult.

Source: Frost & Sullivan.
For more information, visit frost.com.

KATHY BRONSHTEIN ■ *Sudler & Hennessey*

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PATRICK CHASSAIGNE
■ *Medidata Solutions*

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DR. DARSHAN KULKARNI
■ *Kulkarni*

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Phase I through III investigations. In late-phase trials, it is important to focus narrowly on the endpoints being measured and not collect large amounts of superfluous data. In so doing, both costs and resources can be optimized."

Postlaunch: Marketing Research

Patient recruitment is always a challenge in any type of clinical trial, and late-phase research is no exception.

"Careful consideration must be given to the type of medical facility where patients will be treated: for example, walk-in clinics, family practitioners, hospital emergency departments," Mr. Selkirk says. "With late-phase trials, there can often be patient-reported outcomes — for example, quality-of-life questionnaires — so the type of technology used for data capture is an important factor. It is not always possible, nor necessarily preferable, to use electronic or Internet-based data collection systems. Lastly, when measuring health outcomes such as pharmacoeconomics, the appropriate model is not always available. If a sponsor needs to proactively build the model, much time and money will be required up-front."

According to Cynthia Verst, Pharm.D., senior VP, late phase research, at i3 Innovus, one of the key challenges in conducting postmarketing research is ensuring the successful trial participation of community-based practitioners.

"These investigators usually have less

DAVID SELKIRK ■ *Clinimetrics*

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research experience than the academic trialists and require a more streamlined approach to clinical development research in the postmarketing setting," she says. "Protocol and CRF designs, technology, and data submission procedures need to be focused and dovetail seamlessly into the routine practices of these investigators to encourage successful study conduct."

One means of overcoming this challenge and reducing the investigator site burden is through the implementation of site management centers or call centers.

"In-house CRAs can remotely assist sites and provide guidance to these community-based investigators to lessen their burden and be the one-stop shop to encourage successful trial participation," Dr. Verst says.

Another important critical challenge with postmarketing research, especially research entailing observational studies, is the understanding and adherence to global regulatory and ethics committee (EC) requirements.

"Staying current with regulatory and EC requirements that vary significantly from country to country can be daunting," Dr. Verst says. "Recent experience and expertise is of paramount importance to ensure rapid study start up and regulatory and EC compliance."

There is a fundamental need for differentiation, and late-phase clinical studies can help meet that need, Mr. Hall of Quintiles says.

"Pharmaceutical companies need to come to grips with late-phase clinical studies if they are to differentiate their products and build a comprehensive value proposition in an increasingly saturated and payer-dominated marketplace," he says. "If they don't take up this challenge, the payers themselves will be only too happy to step into the breach, and if that happens at the end it will largely come down to price."

Given the FDA's position on REMS, continued growth in late-phase research seems more likely than not, Mr. Selkirk says.

"Many of the pressures that drive late-phase trials, such as price controls, product positioning relative to competitors, safety profiling, and the like will remain in place regardless of the outcome of the U.S. healthcare debate," he says. "These pressures are also international, thereby making the increase in late-phase research a global phenomenon."

Regulators, payers, physicians, and consumers are all concerned about collecting the evidence to demonstrate a product's safety, effectiveness, and value, says Patrick Chassaigne, director, late phase solutions, at Medidata Solutions.

"Ensuring a successful launch and long-term product growth requires comprehensive market intelligence, which is not the purview of registration-based trials," he says. "In addition, regulatory agencies are now requesting that sponsors implement postmarketing studies to continue monitoring product safety and address risk-benefit in a real-world environment."

Designing and implementing these observational studies and registries is challenging due to the diversity of study types, anticipated outcomes, and geographic reach, he says.

Mr. Hall maintains that a paradigm shift is needed in the biopharmaceutical industry.

"Companies need to view postmarketing data as an opportunity to demonstrate value rather than looking at it as a defense mechanism," he says. "In doing so, patients, physicians, payers, and regulators have the data on which to make informed decisions, and the brand has a solid base on which to build trust and differentiate from competitors."

Ultimately it comes down to real life-cycle development, Mr. Hall says.

"Payers drive product usage toward those that have data to demonstrate the greatest improvement in health outcomes for the budget spent," he explains. "The concept of value has widened to encompass not just whether a drug is safe and works, but other key factors, such as how it performs against the current gold standard of care, cost-effectiveness, long-term risk management, and satisfying reimbursement criteria. While elements of value creation, such as patient-reported outcomes or quality-of-life measures, can be incorporated into Phase II or III clinical trials, the real goal of these studies remains getting the drug licensed. It is imperative that this goal is not compromised by building in too many more objectives." ✦

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