

“The Pink Sheet”[®]

Prescription Pharmaceuticals & Biotechnology

November 29, 2010

Volume 72 Number 48 Page 7

Early REMS Assessments Show Room For Improvement In MedGuides

Results from early Risk Evaluation and Mitigation Strategy assessments suggest sponsors have a ways to go before they can show the vast majority of patients receive, read and understand Medication Guides.

Top-line assessment data from eight REMS programs show that a mean average of 83% of patients received the MedGuide, with 70% saying they actually read the document and 63% indicating they understood the key risk messages, according to data from **United BioSource Corp.**

The results also suggest room for improvement in REMS communication plans directed at doctors and pharmacists. Assessments conducted across six programs showed that a mean average of 74% of health care professionals understood the key risk messages.

Kelly Davis, United BioSource Corp.’s VP of safety, epidemiology, registries and risk management, presented the summary data at the Risk Management and Drug Safety Summit in Washington, D.C. United BioSource is involved in implementing evaluations for more than 30 programs.

The FDA Amendments Act requires all REMS include a time-table for submitting program assessments. The standard time-table is 18 months, three years and seven years after approval of the REMS, although FDA can specify other frequencies and has shortened the reporting intervals for drugs with significant safety concerns, particularly those with REMS containing elements to assure safe use.

FDA’s powers to impose REMS took effect in March 2008. As more REMS assessments are coming due, companies and FDA are finding it challenging to evaluate the effectiveness of the risk mitigation programs (“REMS Assessment Is As Challenging As Initial Design, Regulators Acknowledge,” “The Pink Sheet” DAILY, May 12, 2010).

A September 2009 draft guidance on REMS format and content highlighted the need for assessments to include recently collected data (“REMS Assessments Need Very Recent Data, FDA Draft Guidance Says,” “The Pink Sheet,” Oct. 5, 2009).

United BioSource’s summary data came from REMS across different therapy areas, although they are slightly skewed toward central nervous system products, Davis said.

In surveys assessing patients’ receipt and understanding of MedGuides, a mean average of 83% percent of 1,488 respondents across the programs said they received the document, with responses ranging from a minimum of 59% in one program to a maximum of 100% in another.

In answering this question, respondents were given either a picture of the MedGuide or other prompts to help them understand the document to which the question was referring. “This is a confusing question, even though it should be quite straightforward, because patients receive so much other paper from a pharmacy when they fill a prescription that often it’s hard for them to recognize the medication guide,” Davis said.

The percentage of respondents who said they actually read the MedGuide ranged from a minimum of 45% to a maximum of 81%, with a mean average of 70%.

“You will be somewhat dismayed to know that after all the work you spend on developing these medication guides and testing them ... only 70% of patients say they read it,” Davis said. She noted that FDA is now requesting sponsors qualify this number even further by providing the percentage of respondents who read all or part of the document.

There were 28 key risk messages across the eight programs, and FDA requests sponsors provide comprehension scores on each message, Davis said. In her data, 63% of respondents demonstrated that they understood the key risk messages. In one program, only 10% of respondents met this criteria, while the 99% mark was reached in another.

The data show that comprehension may be heavily dependent upon the patient population at which the REMS is aimed.

Two of the eight programs involved schizophrenic patients, who demonstrated less understanding of the key messages than other respondents, thereby bringing the mean average and minimum numbers down across the dataset, Davis said.

Doctors, Pharmacists Score A “C”

Assessment data from six REMS with communication plans for health care professionals showed that a mean average of 74% of 1,347 respondents understood the key risk messages. There were 17 risk messages across the programs, and the responses ranged from a minimum of 17% in one program to a maximum of 99%.

United BioSource believes that ideally, the target should be that “well over 80%” of health care professionals have an understanding of key risk messages, Davis said.

“I think that most of us would like to see this at a higher level especially because we know that many of these risk messages will be related to the most important safety information for the products,” she said. “Many of these products have black box warnings, in fact almost all of them do. Much of this safety information that you’re testing on for REMS messages with communication plans would be information that’s linked to the information in the black box warning, yet you would like to see scores higher than a ‘C’.”

Learning From The Data

Less-than-stellar assessment outcomes do, however, provide an opportunity for improving the content of a product’s label and its REMS.

Among the communication plans assessed, there were a couple of situations where the labeling was unclear, Davis said. The 17% minimum response rate was related to “somewhat confusing” labeling about drug interactions for one product, which was subsequently improved.

Since REMS assessments are still in their early stages, FDA does not appear to be ordering any drastic measures based upon the results.

The agency is currently more concerned about the qualitative, rather than quantitative, results of REMS assessments, said **Novartis Pharmaceuticals** U.S. Safety Risk Director Gary Appio, whose company has gone through two assessments to date. “They’re really not moving to drastic changes when they’re getting these assessments; they’re still feeling their way through it, too.”

When FDA determines some kind of corrective action is necessary, it has generally requested small changes to the MedGuide language and increased education of health care professionals to reinforce risk messages in the label, Davis reported.

United BioSource Senior VP of Safety, Epidemiology, Registries and Risk Management Gerald Faich said the agency has taken a step back from its initial expectation of assessment results.

"Originally FDA was saying we want to see 95% of patients informed, or whatever it might be, and then the survey data starts coming in and we start to move toward a real world," Faich said. "So there is some backing off, I think, on where FDA started out."

REMS Goals And Liability Protection

Speakers at the two-day conference stressed the need to ensure that a REMS' goals are appropriate, not only in terms of assessing their effectiveness but also to protect a company from liability.

Hyman, Phelps & McNamara attorney Josephine Torrente recommended sponsors push back against FDA advice urging the inclusion of REMS goals and objectives that are not within their control.

"I've actually had FDA ask a company to say the company will assure that the pharmacist gives out a MedGuide with every prescription. The company cannot assure that. There is no way. It should never agree to that," Torrente said.

"The company will assure that all pharmacists are properly educated and know that they should do that, you can assure that, but I would push back significantly on assuring things that you are completely incapable of controlling no matter what systems you put in place."

Companies that make a good faith effort to conduct their REMS assessments in a reasonable manner should not worry, at this time, about the agency imposing civil money penalties authorized under FDAAA, she said.

Civil penalties may reach \$250,000 per violation for failing to comply with the requirements of a REMS, up to a maximum of \$1 million for all violations in a single proceeding. Additional penalties may be assessed if the violation does not immediately cease.

Speaking at a Food and Drug Law Institute conference earlier this year, Torrente said there remains great uncertainty about how FDA will impose civil penalties for REMS programs that are not being correctly implemented ("FDA's REMS Stronghold: Industry Sees Need For Alternate Risk Management Plans Beyond Mandatory Programs," "The Pink Sheet," Feb. 22, 2010).

The threat of civil penalties is "a very real hammer FDA can hit you with should you not comply with your REMS or do your assessments, and that has people justifiably nervous," Torrente said.

Conversations with staff in the agency's Office of Chief Counsel suggest that since both FDA and industry are just now learning how to do REMS assessments, "they're not yet looking for the company to make an example out of ... I don't think that's going to happen for a few years," Torrente said.

Speakers at the meeting also discussed the need for sponsors to prepare to discuss REMS at advisory committee meetings even if they have already reached agreement with FDA on the appropriate risk management strategy ("Defensive REMS' May Be Needed To Appease Advisory Committees," "The Pink Sheet," Nov. 29, 2010).

– *By Sue Sutter*