Leveraging **POSTAPPROVAL** Research

The postapproval landscape has changed for pharmaceutical manufacturers.
Strict regulations now require companies to engage in postmarketing safety surveillance; however, data obtained during this time can be used to a company's advantage.

Only a few short years ago, both product management and product marketing were considered relatively straightforward and uncomplicated activities. Sales representatives were more likely to have greater access to physicians and healthcare providers, and fewer restrictions were placed on marketing activities.

"Once a product received regulatory approval, subsequent research activities were generally considered complete, except for activities that looked to expand the product's indication or indications or to explore new avenues for product delivery," says Craig Eslinger, global senior executive director, postapproval services, at PPD.

THE PRESENT: REGULATORY CONCERNS

Recently, the postapproval landscape has changed. With the onset of scrutiny from the Office of the Inspector General (OIG), marketing activities, especially those activities in the realm of late-stage research, have been severely restricted, and many former marketing strategies are no longer allowed.

"Some states are now passing legislation that completely eliminates any or all promotional spending, and sales representatives are finding it nearly impossible to get an audience with their target customers," he says. "To further complicate matters, recent product withdrawals over the past few years have resulted in negative public sentiment not only toward the pharmaceutical industry, but also aimed at the FDA. These withdrawals have tarnished our industry's reputation. Congress and the American public are pushing for new and more effective ways to ensure that products on the market are safe and receive continuous scrutiny. The FDA is now under increased pressure to establish premarket safety as well as postmarketing safety surveillance, and a number of risk-management initiatives are under way to achieve that goal."

Mr. Eslinger cites as an example the FDA's recently revealed "Safety First — Safe Use," a new initiative intended to strengthen the agency's internal processes for managing the safety of drugs on the market. The goal of the initiative is to provide equal consideration and attention to product safety in both the premarketing and postmarketing settings, which will most likely result in an increase in the number and scrutiny of postapproval safety studies.

The industry is also under increasing pricing pressures, and as such he says many providers are now requiring cost-effectiveness data before allowing any products on formularies. In addition, patient-reported outcomes (PRO) — quality-of-life and related types of information, which are obtained directly from patients — is another area of increasing interest to researchers and regulatory agencies. Information on PROs can demonstrate a product's effect on quality of life.

"But obtaining information from patients is becoming more difficult as a result of necessary privacy initiatives, such as the Health Insurance Portability and Accountability Act (HIPAA) of 1996," he says.

REGISTRIES CAN ADDRESS REGULATORY CONCERNS

Mr. Eslinger avers that scientifically rigorous, well-designed, and well-executed registries can address regulatory concerns and research agendas as well as help with the above-noted obstacles.

"As an unintended consequence, registries can build a strong brand, increasing a product and corporation's public persona," he says. "But it's imperative to identify the appropriate observational — epidemiologic — study design to match the regulatory concern or research agenda and to analyze, interpret, and frame registry results in the appropriate scientific context. In addition to information on treatment effectiveness and product safety, observational studies can obtain information on patient-reported outcomes to assess a product's effect on quality of life."

It is widely known that drugs are not 100% safe and that clinical development alone may not provide a comprehensive picture of a product's safety profile. Side effects can appear at a later date for drugs taken for a long period of time or by very large populations. As a result, postapproval research may be a good complement to clinical development.

Mr. Eslinger notes that following the passage of the Prescription Drug User Fee Act and its amendment in 2007, the FDA now has the mandate to require sponsors to conduct postapproval studies. Thus, observational studies conducted for what were once consid-

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Craig Eslinger

Future marketing and product strategies will need to change for a product to be successful. Postapproval research provides a method to address lagging consumer confidence while also yielding valuable clinical and safety information.

Postapproval studies are now required, so company resources should be leveraged to ensure product safety and to provide valid reasons for target customers to embrace our products.

ered to be postapproval commitments can now be viewed as postapproval requirements.

"The number of registries conducted as postapproval commitments/requirements is expected to increase because of recent legislation and increased public scrutiny and congressional interest related to drug safety," he predicts. "When used to support product strategy, a well-planned, executed, and interpreted registry may have a powerful effect on future product adoption and overall return on investment."

THE OPPORTUNITY

"Registries" is an umbrella term representing a number of observational study designs used to address regulatory concerns or research agendas in postapproval, and sometimes preapproval, settings. Mr. Eslinger states that they should only be conducted to answer scientifically valid questions, using methods consistent with the Guidelines for Good Pharmacoepidemiology Practices made available by the International Society of Pharmacoepidemiology, based in Bethesda, Md.

"Registries can be used in a number of roles and functions, such as in hypothesis testing, hypothesis generation, risk-minimization activities, natural history of disease studies to support clinical development efforts, pregnancy registries, product registries, and long-term safety data collection after drug approval," he says. "This list is by no means exhaustive, but illustrates the flexibility of observational studies to support indirectly a wide array of product management and product marketing functions."

Research conducted after a product's approval is different from the controlled environment of research conducted before a regulatory agency's approval. Before approval, research is focused on the product's safety and efficacy and is conducted by experienced investigators in a limited patient population. It is guided by strict protocols with stringent inclusion and exclusion criteria.

"But once a product is approved, it is then studied in the real-world context of normal use under the care of practicing, community-based physicians — i.e., physicians not normally involved in day-to-day clinical research," he says. "The products are used by a broader patient population, which may have other medical conditions and be taking additional medications. This real-world evaluation is the next step of the product's life cycle and needs to be monitored closely for safety signals."

Data collected before approval, immediately after approval, and for the rest of a product's life cycle are valuable because the information can help create credible strategies that support marketing efforts. Real-world research collects data that physicians, healthcare providers, and patients can use to assess their treatment management, increase product adherence, and strengthen a product's place in the marketplace. These data also will be more credible, because the information has been collected by practicing professionals using a product in their practices.

Data collected from these studies can be used to fuel such marketplace activities as:

- Dissemination of evidence-based product information
- Formulary acceptance
- Publication strategies
- Continuing medical education

- Patient adherence programs
- Ongoing product safety monitoring

DISSEMINATING THE DATA

In the past, data collected from postapproval research programs were housed in either the research and development or medical affairs departments. The data were used to direct future and/or additional research but were seldom shared in the marketplace.

"With new concerns related to drug safety, these data should be disseminated not only internally, but also externally to target customers," he contends. "The process of collecting and analyzing these data demonstrates to the marketplace that companies, and the industry as a whole, are doing what is necessary to ensure product safety and proper use. Data collected in the real world are especially pertinent to customers, because they address daily challenges. The data can be presented in the marketplace through journal ads, articles, posters, and presentations at medical conferences."

Mr. Eslinger adds that the communication of this information is also an excellent way of establishing positive, long-term relationships with current and future prescribers. These long-term relationships can help establish product and company image in the minds of end-users and can help leverage current and future products still in the laboratory.

CONDUCTING THE STUDY

Postapproval research studies are commonly conducted by community-based physicians. They must be properly designed and executed to ensure both physician and patient compliance and to produce scientifically valid safety data. The studies must be feasible and kept as simple and brief as possible, because community-based physicians will not have the infrastructure and staff such as seasoned clinical investigators. Companies must also recognize the uniqueness of this type of research and not attempt to mimic clinical research design.

"A sponsor's failure to recognize this uniqueness of observational studies will result in expensive and/or unsuccessful programs and may frustrate site investigators who know the difference," Mr. Eslinger warns. "Clinical objectives must also be understood and incorporated into the programs to ensure a positive experience for both current and potential customers."

As an added benefit, he says all study-related materials, such as patient diaries and Websites, can be branded once the product is approved, as they are effective in raising awareness of the product to potential and participating physicians and patients.

"Although the OIG has made it clear that studies may not be conducted with this intent in mind, it can be viewed as an unintended benefit from having to conduct a postapproval observational study," Mr. Eslinger states.

TECHNOLOGY CAN HELP

Most postapproval research now uses technologies such as IVRS and EDC to eliminate paperwork and help physicians incorporate the program into their daily activities. Technology has improved and is now easy to use, self-intuitive, and requires no special hardware or software.

"Technology interfaces can be branded once a product is approved, for example, a special toll-free number incorporating a product's name or the name of an actual program, the landing page for an EDC collection tool, study specific Websites, and so on," he says. "Study and/or disease-specific Websites can also be a valuable touch point for customers. Posting pertinent information, such as study progress reports and valuable disease specific information, keeps customers interested in the site and will ensure they return to the company's site."

ENGAGE THE EPIDEMIOLOGISTS

Mr. Eslinger suggests that product marketers engage their epidemiology department early and often throughout their programs.

"They will provide valuable input into study design and endpoints and can serve as a resource throughout the entire program," he says. "Epidemiology's input is important in today's regulated environments, because it is instrumental in defining the scientific purpose for a program and in maintaining scientific integrity of the study's conduct and interpretation. The messaging derived from scientific research will be received more readily by the target population if the registry is designed by those with epidemiologic expertise." ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

A DISEASE REGISTRY APPROACH IN PRACTICE

Initiating a disease registry and allowing all patients with the targeted disease to enroll is one way for a company to establish itself as a leader in disease management and treatment. A disease registry helps both the company and the medical community to define the disease and track treatment progress.

In addition, maintaining a registry motivates participation from the treating physician and patients. Since disease registries are open to all patients, comparative data (with current treatments and/or standard of care) can also be collected.

The Genentech Stroke Presentation Survey registry, initiated in 2000, is an example of a disease registry. It is a prospective registry of patients with acute stroke. The study was designed to characterize prehospital delays and delays within the emergency room. It suggested that earlier use of thrombolytic agents is an important factor in the treatment of acute stroke and that interventional programs for potential patients, including stroke recognition and appropriate response, were needed to expedite the receipt of medical attention.

Although the goal of the study was to characterize prehospital delays and delays within the emergency room, the study also demonstrated Genentech's commitment to the registry and the importance and effectiveness of its Activase (alteplase) product to the medical community.

Alternatively, a company can initiate a registry exclusively focused on its own product, which could be used to establish product-specific guidelines and collect outcomes and/or economic data specific to the product. According to the Bruckner Group, almost 100% of managed care organizations and pharmacy benefit managers now analyze a product's value when making formulary decisions. These data also provide a valuable basis to generate best practices, (e.g., patient and/or disease specifics that affect treatment success). Best practice guidance is especially important for a newly launched product where there may be a lack of product knowledge and/or experience with the product. The actual registry itself also gives target customers an opportunity to use a product and then give valuable feedback.