FDAAA: Considerations to Limit Expenditures in Postmarketing Research

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In 2007, the Food and Drug Administration Amendments Act (FDAAA) was signed into law. The act is designed to protect the rights and safety of patients by requiring more comprehensive reviews of new and existing drugs and devices. Prior to FDAAA, postapproval commitment studies were required as part of NDA approval; however, the FDAAA legislation now gives the FDA legal support to request and enforce postapproval studies. Failure to comply with FDAAA risks civil monetary penalties of as much as $10,000, with additional penalties of up to $10,000 per day if violations are not corrected within 30 days.

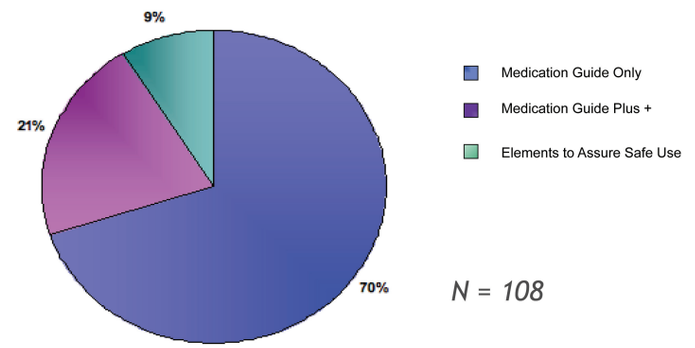
Although the introduction of FDAAA is critical to public health, the signing of the law represents a significant challenge for biopharmaceutical companies, as requirements for increased postmarketing surveillance have necessitated higher levels of expenditure in this area. In this article, we highlight some of the key features of postapproval research, and offer some best practices for creating operational efficiencies that will help biopharmaceutical companies reduce the impact of this regulation and limit the resulting increased expenditures.

An important component of FDAAA is the introduction of Risk Evaluation and Mitigation Strategies (REMS). Previous to FDAAA, RiskMaps were used to evaluate and manage risks of approved products where the potential benefit of the product is significant, yet risks associated with misuse could be harmful. In addition to the development of penalties for noncompliance, REMS created more definition and structure for this type of program. The scope of a REMS can vary from a Medication Guide only to a full limited access program. As seen in Figure 1, the majority of REMS are still Medication Guide only; however the proportion of more robust criteria (such as Medication Guide plus Communication Plan) has shifted over time.

To supplement REMS activities, the FDA now has additional authority to enforce postmarketing requirement and commitment studies. These could include lab and drug stability studies, clinical trials, and pharmacoepidemiologic research programs.

Spring 2010 marks the start of the first 18-month REMS assessments. Figure 2 tracks the increase in the number of REMS due through August 2011. As more and more REMS assessments are due, there are many lessons that industry can learn for best practices in how to conduct a successful REMS assessment while mitigating cost and operational efficiencies.

Figure 1. Current REMS Distribution



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Conducting Postmarketing Research

In the drug commercialization process, postmarketing research can provide unique and valuable data for a wide range of stakeholders, including regulatory agencies, sponsors, and payers, physicians, and their patients.

Important information that can be gathered and leveraged through postmarketing research may include:

- Additional pharmacovigilance data on broader populations and longer duration exposure
- Product uptake and public perception
- "Real-life" practices for treatment of disease
- Health information and education
- Hypothesis generation and publication support
- Collaboration with Key Opinion Leaders (KOLs)
- Health outcomes and economic data
- Comparative effectiveness
- Strategic publication planning

The main types of observational studies that are conducted in the postmarketing environment include disease/product/pregnancy registries, Large Simple Trials (LSTs), Health Outcome and Economic, Safety-Surveillance (including PASS), case control, and cohort studies. Each of these studies brings a unique perspective and provides important information on "real-life" disease progression and treatment.

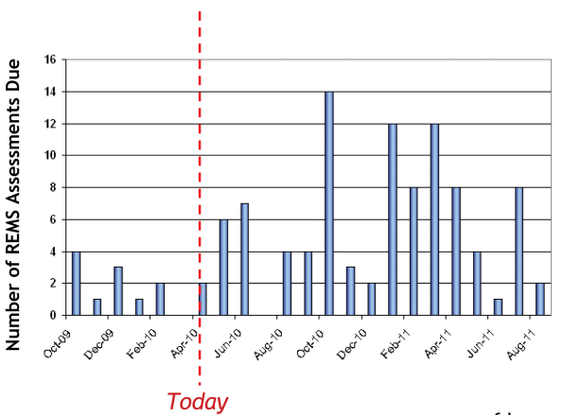
The design of an observational study also plays an important role in the strength and value of the results. Although many postmarketing studies are designed similarly to preregistration studies (Phase 2 and/or 3), postmarketing research offers an opportunity to evaluate a broader population of patients within their usual health care setting. While a clinical trial is usually more internally valid, postmarketing observational research maintains a high level of external validity compared to a clinical trial. In fact, the more restrictions you place on a study design (ie, strict inclusion/exclusion, randomization, mandated treatment parameters), the less likely the results will mimic the actual population in the marketplace. In many cases, sponsors who have designed such studies find that the results are nearly identical to what is seen in the phase 3 setting.

In addition, given that the sample size of many observational studies can reach into the thousands of patients, it is essential to utilize an operational strategy specific to the needs and requirements of this type of research. Applying a phase 2/3 execution model to an observational study can not only influence the noninterventional nature of this type of research, but will also result in unnecessarily excessive expenditures and increased risk of not meeting study objectives.

Below are some additional characteristics of observational research (when compared to clinical trials) that are important to consider when planning your postmarketing studies:

- Noninterventional (observational or "real-life")
- Broad patient population representing actual consumer base
- Large number of sites to indicate practice pattern variances
- Mix of research-naive sites and academic centers
- Longer duration showing treatment fluctuations over time (longitudinal)

Figure 2. 18-Month Assessments



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- Data collection focused on outcome or objective
- Treatment decisions made by physicians based on usual clinical practice
- Data monitoring activities focused on outcomes of interest

In addition, options for data collection are typically more diverse in observational studies than those available in clinical trials. Most postmarketing research still collects data from physicians enrolling patients during the first visit and any subsequent "usual practice" visits. However, since patients may only see their physician on an infrequent basis, it may be necessary to collect ongoing data in the interim. In many cases, patient-identifying information is collected under HIPAA regulations and used for direct follow-up and retention activities, or there may be a collection of retrospective data from medical chart review or claims data. In addition, most post-marketing studies utilize Electronic Data Capture (EDC) technologies to efficiently collect a large amount of data in a rapid fashion.

Planning Ahead

During the planning process prior to project execution, special attention needs to be paid to keeping the program simple and streamlined. Proper planning considerations can reduce unnecessary expenditures and allow budget reallocation to more critical items across the project. As more and more postmarketing and noninterventional studies are conducted internationally, a number of factors need to be considered in order to design the best study possible:

- What criteria were mandated by the FDA-approved REMS?
- Which KOLs are best suited for this study?
- What other nonmandated product questions can we answer through this study?
- Based on the requirements and KOL feedback, what countries will be considered for inclusion of patients?
- What types of physicians and patients will participate in this study? All experienced, study-naïve, or a combination?
- How will required essential documents be collected from physicians, and how will patient data be collected?
- For international studies, based on the countries chosen, what documentation and information will need to be translated and culturally validated for use in the study? What are the noninterventional requirements for each country, and does the study fall under the definition?
- Are any outcome measures being assessed in this study? If so, how are they to be collected – web-based tools, telephone, paper, in-office?
- If Patient Reported Outcomes (PROs) are being used, have the assessment tools been linguistically validated for each culturally diverse patient population?
- What available technologies can be used to help to successfully execute the study and reduce direct and/or indirect costs?

By answering these questions well in advance of executing and managing a postapproval study, you can effectively ensure compliance with the FDA-mandated postmarketing research and a successful study outcome for the sponsor—in the most cost efficient way.

Postmarketing Studies Best Practices

In order to minimize the additional expenditures required to meet the requirements of FDAAA, the first step is to implement effective study start-up processes and procedures for observational research. For instance, when programs are conducted globally, it is vital to ensure that those executing the program understand and abide by the latest regional and country-specific regulations regarding postmarketing and noninterventional studies. For projects that coincide with a product launch, it is also necessary to predict country activations based on the current durations for product reimbursement and approvals.

As a large percentage of the sites participating in observational studies are often research-naïve, it is essential that site qualification, contract execution, essential document collection, and ethics submissions be closely monitored to keep processes on track.

Selecting an IRB

Sponsors are ultimately responsible for all selected study stakeholders associated with postmarketing drug and device studies, including CROs, IRBs and other vendors. Since many sites involved in research are community-based, sponsors may be able to streamline study and site review by selecting to work with a central IRB. Just as rigorous due diligence is conducted in selecting a CRO partner, in-depth consideration needs to be given to the process of selecting an IRB.

Good FDA standing and AAHRPP-accreditation are standard criteria in IRB selection. For postmarketing studies, it is also important to collaborate with an IRB experienced in the unique requirements of observational research. Launching a postmarketing study under the jurisdiction of an inexperienced IRB, only to transition mid-study to a different IRB, can result in additional financial investment into the program. Therefore, it is important to thoroughly investigate IRBs to ensure they have a comprehensive understanding of the postmarketing arena, including protocol design, direct-to-patient follow-up techniques and reporting requirements as mandated by FDAAA.

A common avoidable situation is working with an inexperienced central IRB that considers standard-of-care activities to be research related (when, in fact, the research intervention is the gathering of data rather than use of the test article). This necessitates significant back-and-forth discussion with the sponsor throughout the review process, creating additional study timeline delays.

Benefits of an Experienced IRB

IRBs with experience in post-marketing research understand the importance of providing time and cost savings opportunities to sponsors while balancing quality and regulatory responsibility. Some of these benefits include:

- **Feedback on Protocol Design:** Some IRBs are willing to be informally involved at the time of protocol design. Their regulatory perspective can enhance the study's safety and confidentiality considerations and streamline the formal protocol review process. It is in the IRB's – as well as in the sponsor's – best interest to launch a well structured post-marketing program.

- **Fostering Operational Efficiencies:** The IRB submission process and documentation requirements might be different for postmarketing vs. randomized clinical trials. IRBs can conserve valuable sponsor time and resources by customizing abridged forms and conveying requirements in advance of protocol submission. For instance, consider the difference between a two-page versus an eight-page site submission form, or the possible inefficiencies that would result from requiring investigators to have more research experience than is necessary or useful in a 1,000-site registry study.

- **Streamlining Consent:** The informed consent process for some postmarketing studies may occur outside of the physician's office. Study subjects in some of these scenarios may never see their physician over the course of the study. In situations where remote consent is permissible, seasoned IRBs can work with sponsors to discuss phone and Internet-based consenting options.

- **Accelerated Review Timelines:** One of the most tangible cost savings IRBs can provide to sponsors and CROs is through fast review timelines. Quick start-up is crucial to meeting study timelines, and IRBs operate on review schedules that can range from days to weeks. Since postmarketing studies can involve site quantities ranging from 50 sites to several hundred, sponsors will want to consider IRBs that can absorb a high volume of sites in a short amount of time.

- **Paperless Environment:** Many experienced IRBs have joined the movement towards a

completely paperless industry. Most sponsors and CROs now expect to work with a review board that offers electronic submissions, approvals, and notifications. The direct result is a highly collaborative partnership through a system that encourages transparency, security, and responsiveness. These accelerated notifications complement the already condensed review timelines so the study (and patient data collection) can commence as quickly as possible.

Project Execution and Management

In addition to start-up optimizations, strategies specific to postmarketing research can also be applied to the study execution. These can include remote site management, targeted onsite monitoring, streamlined data management, statistical analysis focused on postmarketing techniques and publications and web-based collaboration to streamline study communication.

Technology Advantages

In today's study environment, it is imperative to take advantage of technologies that streamline communication and transparency with all study stakeholders. This is especially critical for managing global postmarketing studies and operating in a paperless environment.

Technology such as the use of web-based 21 CFR Part 11 compliant electronic trial master files (eTMFs), allow for select sharing of documentation to all study stakeholders and utilized to rapidly execute and close out each study. These eTMF solutions have shown significant cost savings by eliminating the need to ship paper documents to investigative sites and maintaining paper regulatory binders.

It is imperative for study teams to properly manage and report information on these post-marketing studies in a timely manner. Web-based systems provide real-time metrics reporting on stakeholder activity In addition, these systems can also support relationship development: using technologies that have been localized into each investigator's native language demonstrates the sponsor is culturally sensitive. This can make a significant impact when trying to collect data from study-naïve investigators and patients.

Embracing available technologies for study collaboration and management more efficiently moves sponsors toward the goal of meeting the study objectives and– just as importantly –collecting the data required by the FDA. It also aids in sponsors' compliance with the FDA-supported Paper Reduction Act of 1995.

Conclusion

Although compliance with postmarketing requirements may seem like an extreme burden, protection of patient safety is the ultimate goal of this FDAAA law. Careful planning in the earlier stages of drug or device development will allow sponsors and their providers to identify the most effective ways to conduct postmarketing research and limit the resulting increase in expenditures.

Each decision made in the planning, implementation and execution of a postmarketing study has a direct impact on achieving its overall goals. Sponsors' due diligence in study design and ethical considerations will set up the framework for a well structured program. Utilization of web-based systems encourages transparency and effective communication with study stakeholders. The combination of all of these resources not only creates opportunities for time and cost savings but encourages a collaborative and successful program. ■

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