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Finding Added Value in Late-Phase Research



Postapproval studies are becoming bigger and more expensive. As a result, pharmaceutical sponsors are looking at other ways to use the data generated from these studies to create value for their organizations.

Postmarketing studies are becoming increasingly important as regulatory agencies demand more long-term data, which proves efficacy, safety, and quality. But they also are big, expensive, and complicated. Late-phase or registry studies can run for five years or more, compared with the 12 months to 18 months seen for many Phase III trials. This presents significant site and patient retention issues for these longer study durations.

Phase IV studies realized a significant annual growth in complexity as sponsors began collecting more study data to address FDA concerns and differentiate their products, according to a report last year by Tufts Center for the Study of Drug Development.

Experts say responding to the needs of late-phase research requires innovation, enabling technologies, evaluations of cost drivers, and a commitment to achieving data quality through nonstandard techniques.

Pharmaceutical companies in the past looked to do postmarketing studies as quickly and cheaply as possible. Now because studies follow patients longer, sometimes as long as 15 years, and are more complicated, sponsors are asking how the data from these studies can provide value in other areas.

Late-Phase Challenges

1. Postmarketing studies are becoming larger and more complex and have longer follow-up time.
2. Sponsors are challenged to come up with ways to get these studies done as quickly and as inexpensively as possible.
3. Investigator identification and recruitment are becoming more difficult. There are more postapproval studies competing for the same patient population.

STEVE ALBRECHT. CHILTERN. Challenges found in late-phase studies may differ from those found by clinical teams conducting earlier phase trials. Addressing the needs of expanded patient numbers in diverse patient populations is one of the most significant differences and challenges. Establishing the geographic scope and investigator type to meet the required data needs can mean beginning the search for sites with lists of thousands of investigators. Study sizes can range from 20 sites and 100 patients to thousands of sites and tens of thousands of patients.

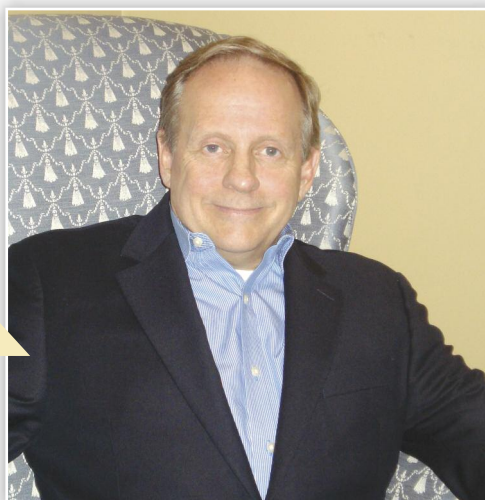
PETER AURUP. MERCK. The biggest challenge of the last couple of years is that regulatory bodies — not just the FDA and the EMA —

have been asking for increased patient numbers for any type of submission. The complexity of clinical trials has increased dramatically over the last few years, and generally regulators are also asking for longer duration of follow up. This all plays into the development programs being bigger and lasting longer. This then feeds into increased competition for good study sites and, ultimately, for patients. We've established a global function that's responsible for all clinical trials, and that gives us very good visibility into everything that goes on wherever the trial takes place in the world. And it also gives us a very clear line of accountability. The global function allows us to reach out to all countries in a region to randomize all of the patients in any type of global program. We can shuffle our resources on the ground and we can optimize our ability to randomize the patients into a particular study.

PEGGY SCHRAMMEL. UNITED BIOSOURCE. Postmarketing studies are often mandated as part of a regulatory commitment, and they can be larger, more complex, requiring more patients and longer follow-up times. It used to be a five-year study follow up was considered lengthy. Now it's nothing to have 10 years to 15 years of follow up required. Another challenge that sponsors are grappling with is how

“ Very large registries can benefit from being implemented in waves or stages, with each subsequent stage building on the previous one. ”

STEVE ALBRECHT / Chiltern



“ Postmarketing studies can show the evolution of how physicians are prescribing and their practice patterns over time. ”

DR. RON CHRISTENSEN / Registrat-MAPI

to execute these studies. Using traditional Phase II/III clinical trial approaches does not work well for a 20,000-patient registry. These are big, expensive, complicated studies. Sponsors are challenged to come up with ways to get these studies done as quickly and as inexpensively as possible. Sponsors are also challenged with how else they might use these data. Many sponsors are saying that the FDA is asking for a 15-year study, and they are looking for other ways the data can be used to show value internally. We are helping them learn how to publish these data and how to pull in other stakeholders to support commercial goals. Sponsors want to show a return on investment on these studies beyond meeting the regulatory mandate.

HANI ZAKI. PRA INTERNATIONAL. One of the biggest challenges for pharma companies is trying to balance their budgets between product registration studies and postapproval work, especially as post-registration efforts are now becoming as important as producing data for the initial registration of products. Postapproval studies can be challenging. For preregistration studies, we know exactly the

hypotheses we are trying to test. In the postapproval arena, the work tends to be more circular, especially when the studies are ‘observational’. At one point in time, there was separation between preapproval and postapproval work. Today, we recognize that there shouldn’t be any separation — it is a continuum. In postapproval studies, we are working to generate the hypothesis; we’re not usually testing any hypothesis. Postapproval studies often are broader, and they tend to take all comers. They tend to not have so many inclusion and exclusion criteria, and in many cases, they tend to be truly observational so that we can monitor what’s happening in the real world.

RON CHRISTENSEN. REGISTRAT-MAPI. Personnel in some biopharmaceutical companies may have limited risk management and observational study experience because of the infrequent requirement for this specific expertise. Instead of performing these activities

internally, they may choose instead to outsource risk management planning or execution of postmarketing requirement studies. Investigator identification and patient recruitment is also becoming increasingly difficult because of the greater numbers of postapproval studies. As a result, there are more research-naïve investigators, and studies conducted within the same therapeutic area are competing for the same patient population. Lack of investigator experience in conducting clinical studies requires sponsor companies, or their designee, to devote more effort to site education and management as well. Investigator remuneration is an issue in postapproval studies because of the competing priority of a busy patient practice and the Medicare/Medicaid anti-kickback statute, which limits compensation to be commensurate with the amount of effort expended. Thus, creating value in postapproval studies is critical, but it generally is not entirely monetary in nature. Value needs to be created in other ways such as through generation of clinically relevant data or improved quality of patient care.

DAVE PROVOST. INC RESEARCH. It’s no longer enough to demonstrate a product’s safety and efficacy. Companies today face the challenge of having to provide health economic and patient-reported outcomes support for their products, and to do so on a global basis. With today’s global launch model, this requires the simultaneous conduct of similarly designed late-phase studies around the world with each designed to meet local needs, which is a difficult and expensive task.

Leveraging Data for Life-Cycle Management

1. Postapproval studies have the ability to collect data that provide insights into products that are otherwise not available and shape a product’s positioning in the marketplace.
- 2: Postapproval studies enable companies to

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“Regulators are asking for longer duration of follow up both before and after product approval. That results in programs being bigger and lasting longer, and that feeds into increased competition for good study sites and patients.”

DR. PETER AURUP / Merck

get the data on the effectiveness, efficacy, and safety of the compound in the real world.

3. Postapproval work can generate some new hypotheses that can lead to clinical development strategies to get additional indications.

ALBRECHT. CHILTERN. Pharmaceutical companies recognize the importance of lifecycle management but often focus on their own brands without taking note of the all-important market life cycle and how this is constantly changing and moving. Companies need to understand how the stages of the brand life span relate to the four stages of the market life cycle. Challenges increase as markets approach the mature and declining stages and generic competition threatens. Some types of data/information about a product are not available before marketing to a larger population. Examples of this include rare adverse events, interactions with other drugs, long-term effects, and effects on patient groups not included in the clinical trials. Therefore, the ongoing collection and analysis of information about a drug after it is brought to market is critical to long-term success. The information gathered during late-phase studies can change the assessment of the benefits and risks associated with a drug. Reimbursement and payer needs can be constantly reviewed and evaluated in a cohesively designed portfolio of late-phase studies. Disease registries can provide a useful baseline of information and a broad-brush view of the market and product positioning. Transitioning from a disease registry to a product registry can provide a powerful combination in gathering a baseline of disease information and care practices and then bridge to examine a specific pharma product in a real-world setting. Studies may be designed to address key reimbursement and

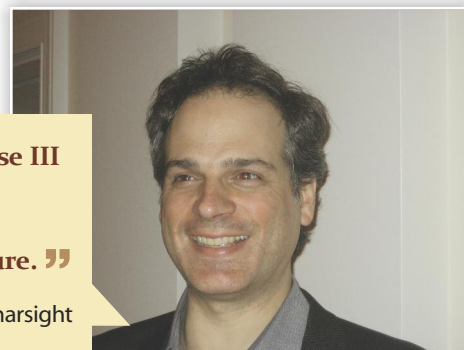


“Postapproval studies may start out to meet regulatory commitments, but savvy sponsors are seeing the benefits of using these studies to support commercial success.”

PEGGY SCHRAMMEL / United BioSource

“Having a successful Phase III study with no clinically meaningful results is still considered a Phase III failure.”

DR. JF MARIER / Pharsight



payer concerns, such as quality and standard of care issues, long-term safety and effectiveness, and quality improvement opportunities.

ZAKI. PRA INTERNATIONAL. The data from postapproval studies are very powerful. The data gained from postapproval studies and subsequent analysis allow companies to manage their products better in the marketplace and to provide better feedback to healthcare providers, to patients, and to payers.

AURUP. MERCK. Postapproval clinical research is very important because it enables us to get additional data on the effectiveness, efficacy, and safety of the compound and continue to build a database of information that can help direct lifecycle management issues or guide new development areas. Postapproval studies, when performed appropriately and correctly and per the highest standards, will typically generate a lot of useful information on a particular compound. In addition, care standards change and develop over time, so what was the standard of care at the time of approval five, six, eight, 10 years ago may not be the standard of care today. To make sure that payers, physicians, and other healthcare providers have timely information that is accurate and reflects the most up-to-date treatment information, postapproval clinical studies likely will continue to play an important role to ensure that such data are provided in a very formalized and structured way.

PROVOST. INC RESEARCH. Well-designed postapproval studies have the ability to collect data that provide insights into products that are otherwise not available. These insights whether efficacy, safety, economic or PRO based, can then be used to shape a product's positioning in the marketplace and guide the development priorities of pipeline products.

SCHRAMMEL. UNITED BIOSOURCE. Sponsors are now putting together pretty sophisticated publication plans from these studies at the time of protocol development rather than waiting 10 years for a final study report. They are also beginning to provide study data to field force teams to help them do their job better. Sponsors are using postapproval data to inform earlier phase trial design, particularly if they have an entire therapeutic area they are focusing on.

CHRISTENSEN. REGISTRAT-MAPI. Postapproval studies can generate hypotheses with new clinical development strategies leading to additional indications or second-generation products. Additionally, postapproval studies can demonstrate inappropriate use or underutilization of a product. Although the product may be suitable and within label for certain patient groups, the product may not be utilized as effectively or as frequently as considered optimal within that population. When this situation occurs, clinical, educational, and marketing efforts can be modified or intensified to address product misuse or undertreated patient populations.

AURUP. MERCK. Having a global function with consistent standards and one centralized global database helps to ensure that the data, wherever and whenever generated go into a centralized database. This enables us to perform timely, distinct, and careful analysis of data sets. At Merck, each compound has its own site, if you will, within the global database. There is a dedicated group that on an ongoing basis looks at and analyzes the data for any and all trends that may emerge as a consequence of all new data being generated. This is done to determine if such identified trends — or signals — that warrant further analysis or if they point to potential gaps in our understanding of the compound and its efficacy and safety profile. If potential signals

are identified, we address those in cross-functional teams that help identify appropriate actions and next steps. Sometimes the data may point to a potential new use of the compound or may point to some areas where we need to better explore the use or profile of the compound.

Best Practices for Late-Phase Studies

1. In general, postapproval studies don't have to be as rigorous. Having more streamlined work processes and SOPs are important for postapproval studies.
2. Companies have to make sure postapproval study designs enable comparative assessment study in an environment that matches actual use settings as closely as possible.
3. Companies should involve pricing and reimbursement specialists along with health economics and outcomes research teams very early on in the product development lifecycle.

PROVOST. INC RESEARCH. Companies have to understand, plan, integrate, and collaborate for postapproval research. Companies need to understand, as best as possible, the future environment into which a product will be introduced: the competition, the regulatory environment, and the payer environment. They should integrate late-phase trial planning into early-phase development planning so that future marketplace challenges are continually discussed and assessed by all development team members. They also need to collaborate on the setting of early- and late-phase research priorities to help ensure R&D efficiencies. Late-phase studies offer the best platform for addressing reimbursement and payer needs. The key, however, is to ensure the use of study designs that enable the comparative assessment of overall treatment costs in an environment that matches actual use settings as close as possible. The real-world applicability of resource use and other health economic-related data collected in studies whose design is not representative of real-world practice patterns can be difficult to assess by those making reimbursement decisions.

ALBRECHT. CHILTERN. Very large registries can benefit from being implemented in waves or stages, with each subsequent stage building on the previous one. This is particularly true of large global registries where regional implementation and management makes practical sense. Implementation in waves can help control resource burn rates, mirror a phased country approval, and better preserve sponsor cash flow for study funding. Well-distributed, country/geographically dispersed teams controlled from a central location can reduce duplication of effort and better control quality. Enabling technologies in the fast-paced world of late phase can focus decision makers on trends and solutions. The appropriate applica-



“ For postmarketing studies, companies should not think in Phase II/III terms. They need to design the study so they operationalize it in a real-world setting. ”

HANI ZAKI / PRA International

tion of tracking technologies can facilitate site enrollment and validation by sponsor teams and track every interaction with sites to allow focus to be brought to recurring issues. Logistics and proven procedures for site operations and activation, recruitment, and data collection method combinations can facilitate rapid and smooth enrollment of large numbers of sites and patients. Greater efficiency in logistics — including recruitment, site management, site and patient retention, and data processing — is essential to control costs. In addition, maintaining quality in large-scale data handling practices is a key to overall efficiency and cost control. Efficiencies can also be realized by using different techniques, such as computer-assisted telephone interviews for data collection.

ZAKI. PRA INTERNATIONAL. Companies should not think of late-phase studies in terms of Phase II/III designs; instead they need to allow the optimal acquisition of the data to dictate the study and format the structure with which they operationalize the execution of the study. There is a need for a larger tool set, especially as postapproval studies become bigger, broader, and require different types of management and monitoring. Sponsors need to have a different approach when they look at these new observational/noninterventional studies.

CHRISTENSEN. REGISTRAT-MAPI. Pharma or biotech companies often use their SOPs from development rather than developing more streamlined SOPs for postapproval studies. Those work processes are probably more appropriate for late-phase preapproval trials than for post approval studies. In general postapproval studies don't have to be as rigorous. Having more streamlined work processes and SOPs are important. Some companies use the clinical trial group to do postapproval studies as opposed to having a dedicated medical affairs group to do the postapproval work. If you have a dedicated group to do postapproval studies, then they get to know the nuances of this type of study. There is a big difference between doing a controlled clinical trial and an observational type of study like a registry.



“ Companies today face the challenge of having to provide health economic and patient-reported outcomes support for their products, and to do so on a global basis. ”

DAVE PROVOST / INC Research

SCHRAMMEL. UNITED BIOSOURCE. To maximize value, companies are looking at other endpoints that can be put into these studies to help show value. One of these is reimbursement. I recommend strongly that sponsors get a pricing and reimbursement specialist along with their health economics and outcomes research teams involved early on in the product development lifecycle and particularly as they are looking at postapproval studies and begin to look for options at collecting data, understanding what data payers are going to require for pricing and reimbursement decisions, and build these factors into the study designs.

JF MARIER. PHARSIGHT. Late-phase and Phase III studies are conducted to confirm what has been learned. The key element is learning as much as possible in early development and then applying what's been learned using a model drug development approach and validating these models in a 'learn and confirm' paradigm. Once there is a set of models, sponsors can make predictions and refine their models based on Phase IIB data. The challenge of Phase III studies is to gather the right amount of information so that the model can be constructed to make predictions about the success of the Phase III trial. And if companies do their homework, the likelihood of success in Phase III trials will be higher. **PV**