Denise Myshko

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.

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

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 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

FEATURED THOUGHT LEADERS

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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. ”**
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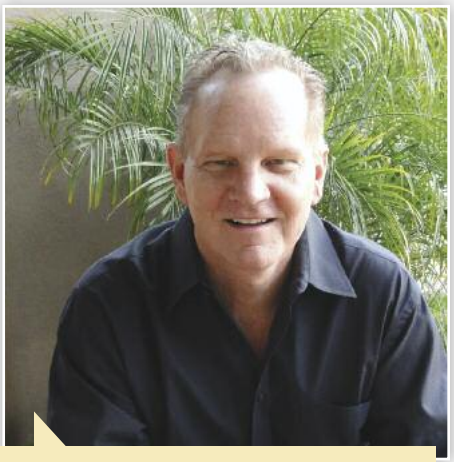
> **DR. PETER AURUP** / Merck



> **“ Postmarketing studies can show the evolution of how physicians are prescribing and their practice patterns over time. ”**
>
> **DR. RON CHRISTENSEN** / Registrat-MAPI

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 post-approval 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 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 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.

> "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

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 application 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

SOUND BITES FROM THE FIELD

Industry experts discuss how comparative effectiveness research can be used to address commercial goals.

SPENCER GOLDSMITH is President of Harvard Clinical Research Institute, a provider of clinical trial services. For more information, visit hcri.harvard.edu.

"Comparative effectiveness research can be a scary proposition for manufacturers because the results may not be favorable to their product. This is particularly true in the case of old-line treatments or therapies that may have become dated. Comparative effectiveness studies offer an opportunity to reevaluate medicines and practices and thereby change or modify current practices. Practicing physicians pose these questions every day as they work to better understand the products that are available. Therefore, the best way to answer these questions is through physician-designed studies that use good science and are peer reviewed."

LAURIE HALLORAN is CEO of Halloran Consulting Group, a life-sciences consulting firm. For more information, visit hallorancg.com.

"Through comparative effectiveness research, companies have an opportunity to demonstrate enhanced value to patients, providers, and payers. Comparative effectiveness research can improve healthcare and evolve R&D, but the industry needs to take a broader view and focus on improving specific outcomes. We are on the verge of major breakthroughs, but more needs to be done through optimized trial design with integrated biomarker development. Without these changes, comparative effectiveness gaps will be as harmful to a new product as safety or efficacy issues."

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.

> "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

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.

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.

> "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

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

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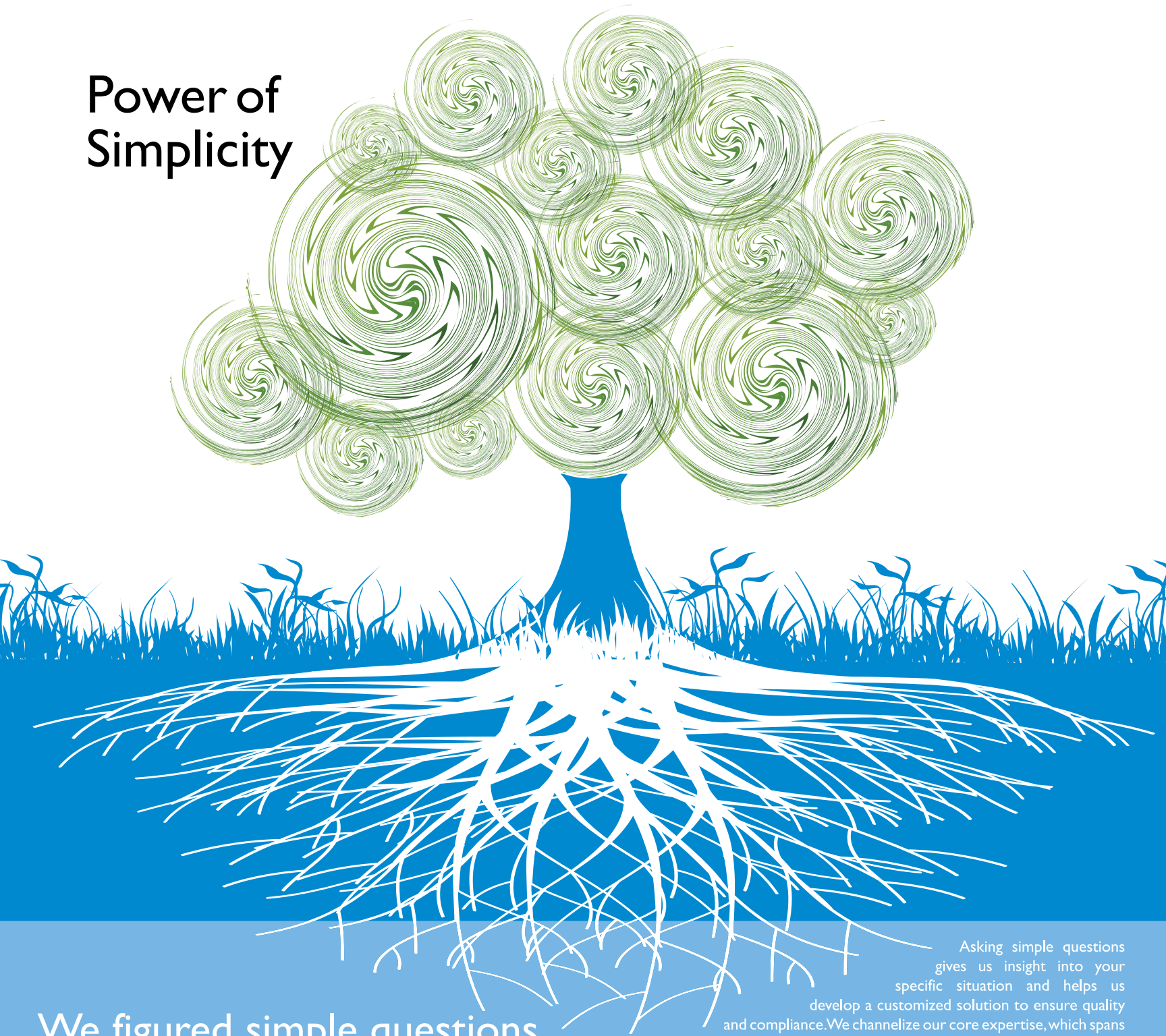

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Denise Myshko

Addressing Phase III ATTRITION

Experts agree: a key component of reducing R&D costs is terminating unpromising products sooner in the development stage. But companies are still struggling with failures as late as Phase III trials.

» **NEWS ITEM:** In February 2011, AstraZeneca announced that the Phase III study of zibotentan monotherapy in patients with non-metastatic castrate resistant prostate cancer was stopped following the results of an early efficacy review.

» **NEWS ITEM:** In January 2011, Sanofi-Aventis and its subsidiary, BiPar Sciences, announced that a randomized Phase III trial evaluating iniparib (BSI-201) in patients with metastatic triple-negative breast cancer did not meet the prespecified criteria for coprimary endpoints of overall survival and progression-free survival.

» **NEWS ITEM:** Antisoma announced in January 2011, that AS1413 was discontinued after Phase III trial missed the primary endpoint for the treatment of secondary acute myeloid leukemia.

» **NEWS ITEM:** In December 2010, Pfizer discontinued trials of Thelin for pulmonary arterial hypertension and voluntarily withdrew the product from the markets where it was approved the European Union, Canada, and Australia.

» **NEWS ITEM:** In November 2010, Novartis discontinued ASA404 after results from a Phase III trial showed the product failed to meet the primary endpoint of extending survival for the second-line treatment of non-small cell lung cancer. Novartis had partnered with Antisoma for the development of this product.

» **NEWS ITEM:** In November 2010, Bristol-Myers Squibb and Pfizer announced that the companies had discontinued a Phase III clinical trial in patients with recent acute coronary syndrome treated with apixaban or placebo in addition to mono or dual antiplatelet therapy.

THOUGHT LEADERS

PETER AURUP, M.D. VP, Head Global Clinical Trial Operations, Merck & Co. Inc., known as MSD outside the United States and Canada; Merck is a global healthcare company providing prescription medicines, vaccines, biologic therapies, and consumer care and animal health products. For more information, visit merck.com.

JF MARIER, PH.D. VP and lead scientist, North America, Pharsight, a provider of software products and consulting services to pharmaceutical and biotechnology companies. For more information, visit pharsight.com.

These are just a few of the most recent examples of product failures in Phase III clinical development. Sponsors both large and small are plagued by these failures, often for efficacy reasons.

Success rates throughout drug development continue to decline. The number of terminations in Phase III development doubled from 2007 to 2009 compared with those in the 2004 to 2006 timeframe, according to a report last year by CMR International.

"When we start looking at these Phase III failures and dissecting the data, there are a significant number of Phase III studies that have been discontinued because of the lack of efficacy of candidate products vs. placebo," says JF Marier, Ph.D., VP and lead scientist, North America, at Pharsight.

Dr. Marier says current research on the drivers of attrition indicates nearly 50% of these studies fail because the candidate product did not demonstrate better efficacy than placebo.

"This suggests that the exposure-efficacy relationship of the product was not well understood in Phase II studies and that patients may have been given a sub-therapeutic dose," he says. "This typically suggests that adequate analyses were not performed with clinically meaningful parameters for the maximum effect of the product."

He also says the lack of differentiation versus other drugs currently available to pa-

Increasing Efficiency of Trials

Drug developers can tap a number of home–grown approaches to increase R&D efficiency. While animal models are useful, they rarely predict the effect of new drugs on human patients. Surrogates can play a role in new drug investigations, but they are difficult to employ and haven't yet cut costs significantly.

New approaches that may help increase R&D efficiency include:

- Reducing distinctions between phases — Traditional distinctions between clinical phases is a matter of practice and not a legal requirement. Starting human trials earlier may offer a way to save money and time.
- Engaging in collaborative relationships — Agreements between sponsors may help accelerate research.
- Using adaptive clinical trials — While the concept is attractive, the FDA has yet to provide definitive guidance, and experience has shown that product development times have not decreased.
- Conducting trials overseas — Creating the oversight infrastructure tends to offset cost savings.
- Selecting the right patients — Improving the definition of disease subtypes and better alignment of subjects for clinical trials can help to prove or disprove the hypothesis sooner rather than later.
- Using exploratory INDs — This relatively new type of pre-Phase I clinical trial, which lets sponsors evaluate up to five chemical entities or formulations simultaneously to identify a lead compound, has not been widely adopted.
- Creating a "company within a company" — This approach transfers newly discovered compounds to a smaller, leaner organization within the larger entity to fast track development to the proof-of-concept stage. Making the go/no-go decision based strictly on the science is also key to saving costs.
- Adjusting the internal reward system — For example, in one large pharma, once the R&D team has taken a new drug to proof of concept, a business unit, either inside or outside the company, "buys" it. The R&D team then shares in profits following commercialization.

Source: Tufts Center for the Study of Drug Development. For more information, visit csdd.tufts.edu.

tients explains another 25% of late-phase trial failures.

"If we dissect the Phase III attrition data further, there is a lack of differentiation vs. comparator products," Dr. Marier says. "In this case, if a drug product candidate meets all of the technical endpoints, the Phase III trial will still be considered a failure because it is not superior to the active comparator.

"This is a sign that the homework was not done earlier in the drug development process," Dr. Marier says. "For example, a product can fail to demonstrate superior efficacy while demonstrating superior safety as compared with an active product. Conversely, a product can fail to demonstrate superior safety while demonstrating similar efficacy as a comparator product. Companies need to raise the bar. They shouldn't just want to have a drug candidate that is superior to placebo; they should want to develop a product that is either more efficacious or safer as compared with other products."

At Merck, the company does a very careful analysis of the data to assess Phase III failures, says Peter Aurup, M.D., VP and head of global clinical trial operations at Merck & Co.

"We do a careful post mortem and look for lessons learned and ways of addressing potential issues early," he says. "Late-phase attrition is painful, and early on we need to — with a high probability of success — be able to sort the winners from the losers from an R&D productivity point of view."

One of the things Merck executives are doing to address this issue is to increase the use of biomarkers, as well as using modeling and simulation techniques, which help guide the decision process.

"We also are trying new statistical approaches, including adaptive trial design, which will enable us very early on to get confirmation on certain predefined signals and then either drop certain studies or parts of a study much earlier on," Dr. Aurup says. "A senior cross-functional team also looks at the entire portfolio and conducts an ongoing prioritization. Phase III attrition is something no one wants to see, but it happens. We are doing what we can to maximize the opportunities to identify those aspects that may trigger a termination of a Phase III program early on in Phase I and Phase II." PV