

The Value of PHASE IV

POSTMARKETING RESEARCH CAN BE CRUCIAL

for tracking side effects and exploring new uses for an approved drug. **BUT THESE TRIALS ARE HEAVILY SCRUTINIZED** because some say pharma companies have conducted such studies purely for promotional purposes with little scientific value.

Phase IV trial results can help differentiate a product from its competitors, medically support marketing objectives and messages, enhance relationships with clinical investigators and key opinion leaders, increase physician exposure to a new drug, answer scientific questions, and provide other helpful information for multiple stakeholders such as patients, physicians, managed care, and disease groups.

PhRMA reported in 2002 that the rate of spending for Phase IV research increased by 20%, and CenterWatch estimates that sponsor spending on postmarketing clinical grants is rising faster than grant spending for Phase I to Phase III studies.

Questions have arisen about the design of these studies. Critics claim that many Phase IV studies serve little scientific purpose and are primarily conducted as a marketing tool. Some say marketers use postmarketing trials as a way to increase market penetration by influencing the treatment choice of health providers and encouraging the product's inclusion in HMO

formularies. The industry is addressing Phase IV trial design and developing best practices to create postmarketing studies that balance marketing and science.

DR. BILL MASSEY



If a study is being done that **DOES NOT IMPROVE PATIENT CARE OR PRODUCT UTILITY, IT SHOULDN'T BE DONE.**

Breaking Down Phase IV

RUFFOLO. There are a couple of types of post-marketing studies that companies do. One is quite important: to find new indications for drugs. A number of very important uses of a number of drugs on the market weren't the first indications approved. They were indications that drug companies found after the original approval. Then there are other studies that are for marketing purposes. Wyeth and other companies are starting to do fewer of those than before. At Wyeth, we are trying to get all post-marketing studies under one umbrella and done to the same standard.

BRADSTREET. Fifteen years ago, differentiations were made between Phase IV studies, Phase V studies, and other periapproval studies.

Today, everyone seems to lump all the periapproval studies under one term: "Phase IV." Phase IV studies are only one of a number of periapproval studies prevalent in today's pharmaceutical industry. Other periapproval studies include marketing surveys, retrospective and prospective patient registries, and product or disease registries. Phase IV can be defined as a postapproval study, designed for something other than developing data to support a new indication. While other periapproval studies have a dual focus of collecting safety data and providing marketing support, a true Phase IV study differs inasmuch as it is carried out mainly for the purpose of risk management and safety data, with a possible "side-effect" of support for marketing strategies. Sometimes Phase IV studies are implemented to re-evaluate results of previously performed controlled clinical trials.

CLAGHORN. About 10 to 15 years ago, studies that were sponsored by a pharmaceutical company were automatically dismissed. We fought really hard to get out of the hole that we had gotten into, and now we are starting to see the scales tip back again. We don't live in a utopian society where the NIH has billions of dollars to fund needed research.

VERST-BRASCH. Marketing practices are coming under greater scrutiny with regard to postmarketing studies. Recent media coverage has led to elevated scrutiny, which unfortunately has cast a dim light on the Phase IV arena.

O'CONNELL. There are some Phase IV trials that are more marketing oriented. Those applications are sometimes referred to as formulary-acceptance trials and provider-experience trials.

A POST-PERSPECTIVE

PATRICIA BRADSTREET. President and CEO, The Bradstreet Group, North Brunswick, N.J.; Bradstreet Group, which includes Bradstreet Clinical Research and MEDdia HealthCare Communications, provides clinical-research and regulatory-affairs services to pharmaceutical, medical-device, and medical-education companies. For more information, visit bradstreetcra.com.

C. DAVID CLAGHORN, PHARM.D. Medical science liaison III, Chiron BioPharmaceuticals, Chiron Corp., Emeryville, Calif.; Chiron is a global pharmaceutical company that leverages a diverse business model to develop and commercialize high-value products that make a difference in people's lives. For more information, visit chiron.com. (Dr. Claghorn's comments are expressly his own and do not represent the philosophy of Chiron Corp.)

RICHARD GLIKLICH, M.D. President and CEO, Outcome Sciences Inc., Cambridge, Mass.; Outcome Sciences is a healthcare-information services company that provides Web-based data management for Phase IV studies and patient registries. For more information, visit outcomesciences.com.

GENE GUSELLI. CEO, InfoMedics Inc., Woburn, Mass.; InfoMedics' technologies fuel pharmaceutical product sales by using the experiences of physicians' own patients to demonstrate that a drug is performing well in the real-world setting. For more information, visit infomedics.com.

DENISE M. KRAPF. Director of business development, LifeTree Technology, Temecula, Calif.; LifeTree, a member of the FFF Enterprises family of companies, offers clinical services and Web-based electronic data capture for accelerating clinical research for trials, patient registries, and surveillance projects. For more information, visit lifetree-tech.com.

JAAP W. MANDEMA, PH.D. Senior VP, chief scientific officer, Pharsight Corp., Mountain View, Calif.; Pharsight develops and markets integrated products and services that enable pharmaceutical and biotech companies to achieve significant and enduring improvements in the development and use of therapeutic products. For more information, visit pharsight.com.

BILL W. MASSEY, PH.D. Managing partner, Scientific Commercialization LLC, Phoenixville, Pa.; Scientific Commercialization provides innovative scientific, technical, and product commercialization consulting to the healthcare industry that enables its customers to maximize their commercial success. For more information, visit scientificcommercialization.com.

MICHAEL O'CONNELL, PH.D. Director of biopharmaceutical solutions, Insightful Corp., Seattle, and is affiliated with Waratah Corp.; Insightful provides enterprises with scalable data and text analysis solutions that drive better decisions faster by revealing patterns, trends, and relationships. For more information, visit insightful.com.

ROBERT R. RUFFOLO, PH.D. President, research and development, Wyeth Pharmaceuticals, and senior VP, Wyeth, Madison, N.J.; Wyeth is

a research-based, global pharmaceutical company responsible for the discovery and development of some of today's most innovative medicines. For more information, visit wyeth.com.

CYNDI VERST-BRASCH, PHARM.D. VP, global medical affairs, marketing and communications (MAM&C), Kendle International Inc., Cincinnati; Kendle is a global provider of clinical-research and development services for the pharmaceutical and biotech industries. For more information, visit kendle.com.

JEFFREY WHITE, PHARM.D., M.S. Director of research services, Prescription Solutions, Costa Mesa, Calif.; Prescription Solutions is a pharmacy and medical management company managing the prescription drug benefit of commercial, Medicare, and governmental health plans, as well as those of employers and unions. For more information, visit rxsolutions.com.

HANI ZAKI, MPH, MBA. Executive director, business development, Phase IV Division, PharmaNet, Princeton, N.J.; PharmaNet provides a range of clinical-development and consulting services to the pharmaceutical, biotechnology, and medical-device industries. For more information, visit pharmanet.com.

JEROME B. ZELDIS, M.D., PH.D. Chief medical officer and VP, medical affairs, Celgene Corp., Warren, N.J.; Celgene is a pharmaceutical company with a focus on the discovery, development, and commercialization of small-molecule drugs. For more information, visit celgene.com.

These programs have a bad rap, and the drug companies have been accused of seeding the marketplace with these types of studies. I see a lot of value in these trials, actually formulary-acceptance trials typically involve fairly detailed pharmacoeconomic analysis, and provider-experience trials can engage physicians and create more awareness of the effectiveness of therapies in the clinic.

WHITE. We have been approached by several pharmaceutical manufacturers to conduct “seed” studies. These studies are usually intended to increase use of a manufacturer’s product and sometimes lack scientific integrity. There is usually a marketing component to these studies, and by doing them the pharma companies get to speak with the doctors about a product and ultimately get them used to prescribing it. The intent is to influence physician and patient behavior.

MASSEY. The vast majority of the time the source for funding a study has absolutely no impact on its scientific validity. After a drug is approved, there is usually continued clinical development that supports the life-cycle strategy for the brand. The funding for clinical studies may come from a variety of internal — clinical, commercial, etc. — and external — NIH, various foundations, etc. — sources. These studies generally are targeted toward obtaining new indicated uses and providing important health economic data that were not obtained during Phase III. In addition, many companies will conduct a study to provide a controlled environment that enables physicians to obtain experience with using the product.

Separation of Marketing and Science

BRADSTREET. There has always been a certain divide between the “scientists” and the “business people.” Striking a balance between the needs of science and the needs of business is an ongoing challenge in all areas of the pharmaceutical industry, not just Phase IV studies.

CLAGHORN. Within certain companies, marketing exerts undue influence on Phase IV studies by rejecting good ideas because they are not what they want to do. Often interesting ideas are rejected, even if there is a business need for them because this is not the direction that marketing wants to take a drug.

ZELDIS. Many pharmaceutical companies have the Phase IV development as part of their marketing department. At Celgene, we purposely put Phase IV and medical development in the medical-affairs department, which is separate from marketing. While we don’t do things in isolation and we do consult sales and marketing, marketing doesn’t drive the whole process.

RUFFOLO. At the moment, preapproval studies and postmarketing studies are under sepa-

rate roofs at Wyeth, but we are in the middle of restructuring. Clinical R&D, which normally does Phase I, II, and III trials, and medical affairs, which usually does clinical trials to support marketing, are going to be moved under one umbrella.

MASSEY. Marketing has value to add in the design of Phase IV trials. If there are clinically meaningful and scientifically valid data to show how one drug compares with another, it is perfectly acceptable for marketing to expound upon these scientific messages.

VERST-BRASCH. Sponsors have varying needs relative to scientific and marketing objectives for their clinical Phase IV studies. The Office of Inspector General regulates the conduct of Phase IV postmarketing studies as well as the industry’s interaction with prescribers and reimbursement agencies. Within Kendle’s medical-affairs marketing and communications group, there is a mix of scientifically focused studies and studies that include some marketing elements.

ZAKI. It can be argued that any study done after market approval is an integral part of life-cycle management and can therefore support marketing activity. Even risk-assessment studies or pharmacoepidemiology studies can have a direct commercial impact on a product. Studies that evaluate safety and best use of the product will obviously impact the product commercially. But, pure commercial activity under the guise of Phase IV is not an acceptable practice.

MANDEMA. In the end, any trial that is being run needs to be designed to show benefits supporting a drug’s specific use or specific claim. Marketing plays a key role in finding out which benefits will have the most commercial value.

WHITE. Marketing should be involved and have influence in Phase IV studies. Typically, marketing supports postapproval research. Marketers are very knowledgeable about the product and understand the issues relevant to the therapeutic area. Even though marketing managers are confident in their product and believe their product has value, their interest should be to conduct a study that is clinically relevant and scientifically sound to provide value to the healthcare community in general. Then the recipients of the data — the healthcare decision makers, the clinicians, managed care, health plans — can evaluate the study and make a decision about the clinical relevance and value of a product.

MASSEY. Ultimately, if the study is designed



DR. RICHARD GLIKLICH

PHASE IV STUDIES HAVE THE CAPACITY TO ADD TO THE SCIENCE AND EVEN POTENTIALLY IMPROVE QUALITY WITHIN DISEASE AREAS.

This reflects positively on sponsors as knowledge partners. If a trial uses marketing dollars appropriately and with the right design, the role of marketing shouldn’t be criticized just because the marketing department may have the money to fund Phase IV studies.

TRIAL DESIGNERS SHOULD ENSURE THAT PHASE IV TRIALS ARE POWERED ADEQUATELY to unambiguously answer specific questions of the benefit of one treatment option versus another.



DR. JAAP MANDEMA



IF MARKETING TEAMS LOOK AT THEIR PHASE IV STUDIES AS A WAY OF RECRUITING QUALIFIED INVESTIGATORS

for upcoming Phase I to Phase III trials, they are contributing to the development function as well as playing a promotional role.

appropriately, a company will get data that are going to help improve patient care and that should be the goal of everyone involved. Marketing can get the data it needs to support product messaging by working with clinical and letting clinical design the study. A clinical staff can design studies that are scientifically valid and that support the messages that marketing wants to get out.

BRADSTREET. The limited number of patients that receive a drug during the preapproval stages makes it imperative that late-stage studies be conducted to supplement the safety data

available at the time that a new drug is approved. It is now par for the course that FDA approvals mandate some type of Phase IV study. Whatever critics may have to say about the role of marketing in Phase IV research, these studies play a vital role in terms of safety and outcomes data collection.

Best Practices for Postmarketing

KRAPF. What comes out of a Phase IV study is as good as what goes in, in terms of the questions asked and endpoints targeted. The clinical leaders participating in the study should be encouraged to ask meaningful questions that will enhance the understanding of the benefits of the drug. Protocols should be developed to yield information that will help physicians and patients make better-informed decisions. From the aspect of personalized medicine — finding the right drug for the right person at the right time — Phase IV studies can make significant contributions.

MASSEY. Phase IV trials should be designed to meet medical needs first and then to support the marketing messages the commercial stakeholders want to communicate.

RUFFOLO. Phase IV studies should be designed similarly to Phase III studies. Researchers should generate a hypothesis, design a study to test the hypothesis, and then power the study in terms of patient size to pro-

Federal Mandate for Ethical Postmarketing Research

In May 2003, the Office of the Inspector General (OIG) issued compliance-program guidance for pharmaceutical manufacturers. The guidance is a major initiative of the OIG's effort to engage the healthcare community in preventing and reducing fraud and abuse in federal healthcare programs. The purpose of the compliance-program guidance is to encourage the use of internal controls to efficiently monitor adherence to applicable statutes, regulations, and program requirements.

With regard to research funding, the OIG suggests that postmarketing-research activities should be especially scrutinized to ensure that they are legitimate and not simply a pretext to generate prescriptions of a drug. The OIG advises manufacturers to develop contracting procedures that clearly separate the awarding of research contracts from marketing. Research contracts that originate through the sales or marketing functions — or that are offered to purchasers in connection with sales contacts — are considered particularly suspect by the OIG.

In addition, with regard to educational and research funding, payments to physi-

cians by pharmaceutical companies for research services should be fair market value for legitimate, reasonable, and necessary services. Manufacturers should determine if the funding is based in any way, expressly or implicitly, on the physician's referral of the manufacturer's product. This could be considered a kickback.

Examples of questionable research include research initiated or directed by marketers or sales agents; research that is not transmitted to, or reviewed by, a manufacturer's science component; research that is unnecessarily duplicative or is not needed by the manufacturer for any purpose other than the generation of business; and postmarketing research used as a pretense to promote product.

Manufacturers are recommended to develop contracting procedures that clearly separate the awarding of research contracts from marketing or promotion of their products.

Source: Department of Health and Human Services, Office of Inspector General, Washington, D.C.: Federal Register, Vol.68, No. 86, May 5, 2003 — OIG Compliance Program Guidance for Pharmaceutical Manufacturers. For more information, visit oig.hhs.gov.

vide a result. Any study should be designed to truly advance the science.

MANDEMA. A best practice to ensure a better trial design is to take a quantitative approach by determining, before the trial is started, the probability that the drug in question can achieve certain potential benefits relative to other treatment options. Sponsors then should quantify the value of those potential benefits for the patient population. This will ensure a trial strategy that has the highest likelihood of confirming valuable treatment benefits.

GLIKLICH. The value of a Phase IV study should be to increase disease knowledge. To achieve this result, a Phase IV study's focus can be on the product but only within the context of the disease. Phase IV studies should be designed to collect data from representative populations that might be excluded in earlier phase trials. Furthermore, ideally the technology used should be able to provide immediate feedback, benchmarking, and best-practices information back to the participating investigator sites to increase the knowledge value of the study to the site. In doing so, the trial is much more about the disease. This may lead to increased prescriptions for the sponsor's particular drug as a result of the practitioners realizing that the drug or the class of drugs provides a benefit to their patients. We believe this impact to be the greatest when the practitioner sees real-time feedback from his or her own clinical practice.

VERST-BRASCH. Some of our best practices to create fair, balanced postmarketing trials include having a compelling scientific endpoint. Yet at the same time, these studies incorporate marketing needs. The scientifically compelling endpoint is important from a regulatory perspective, as well as to create physician interest and aid physician recruitment. The study has to lend itself to the overall development of a particular area of healthcare and contribute positively to a particular indication.

O'CONNELL. One best practice would be to involve thought-leader physicians and or biostatisticians in the design of the trial. It is really beneficial if physicians can see first-hand data on the efficacy and the effect of the trial. That can sometimes be interpreted as a marketing ploy, but having thought-leader physicians and biostatisticians involved on a scientific level can really help the integrity of these trials.

Real-World Challenges

ZAKI. The ultimate challenge facing any Phase IV program is assuring that the studies advance scientific knowledge and enhance medical and commercial value all at the same time. Pulling this all together into a program is a real challenge. The Phase IV environment is very strategic and creative and more often than not there

are no boilerplates. Developing Phase IV programs necessitates drawing on a lot of ideas from a lot of disciplines to get to a design that answers the questions a pharmaceutical company is seeking.

Phase IV study designers have to determine whether the program will withstand regulatory rigor. We take a collaborative approach to help sponsors navigate smoothly through the complex Phase IV study environment and **ACHIEVE THE APPROPRIATE SCIENTIFIC/MARKETING BALANCE, WHILE ENSURING REGULATORY COMPLIANCE.**

WHITE. The overall challenge to conducting Phase IV research is striking a balance between the scientific rigor of the study design and the relevance to real-world practice. Phase I, II, and III clinical trials may or may not be relevant to real-world outcomes. These studies are designed to determine whether a drug can achieve a predetermined clinical marker or has a safety issue. Conducting research in the real world poses a different set of issues. Striking a balance between clinical relevance and scientific integrity is a real challenge, but very important.

O'CONNELL. The challenge for Phase IV trials is to demonstrate a sound clinical outcome that adds knowledge to the use of a drug in the market. Studies that show superior efficacy for particular subpopulations are very interesting. These studies can document real-world outcomes of a drug in patient populations beyond the clinical-trial study group.

GUSELLI. We have pioneered the use of patient-experience programs, which reflect how patients, in a real-world practice setting, respond to a medication. Patient-experience programs concentrate on effectiveness measures, such as issues related to symptom relief resulting from the medication, onset to relief, quality of life, intent to continue use of the medication, convenience factors, and compliance. This patient-derived



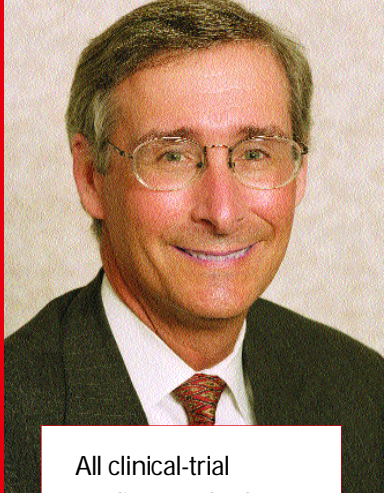
DR. CYNDI VERST-BRASCH



GENE GUSELLI

PATIENT-EXPERIENCE PROGRAMS ARE DRIVEN BY INDIVIDUAL PATIENT EXPERIENCES and the perceptions that a patient has about a medication therapy.

DR. ROBERT RUFFOLO



All clinical-trial studies — whether they are Phase III or Phase IV or company or FDA initiated — should be held to the **SAME HIGH STANDARDS FOLLOWED FOR PREAPPROVAL TRIALS.**

DR. JEROME ZELDIS



Phase IV trials can be more substantive and less focused on marketing objectives if the trial designers understand why a Phase IV study is being done and what the study is trying to accomplish. **THE MOST MEANINGFUL STUDIES ARE RANDOMIZED PLACEBO-CONTROLLED, OR RANDOMIZED PROSPECTIVE-CONTROLLED TRIALS.**

information is reported back to physicians to provide their practices with a mechanism to monitor patients' tolerability and satisfaction with the medications they're taking. The data provided to physicians recognizes the broad, heterogeneous patient population physicians are presented with every day, which contrasts with the narrow populations in a clinical trial. These data are more reflective of the decisions physicians face on a daily basis about their patients' treatment.

MANDEMA. Balancing marketing needs with the scientific or clinical profile of the compound in question is the biggest challenge.

VERST-BRASCH. The challenge of designing Phase IV studies is appropriately identifying and incorporating not only unmet scientific needs but also unmet marketing needs, while meeting regulatory requirements. Trying to strike that delicate balance between the two is often very difficult within the industry, especially in the late-phase arena, because it involves the effective integration of medical affairs and marketing functions. This is difficult because both functions are incredibly diverse, backgrounds are different, the reward structure is different, and there are different expectations and definitions of success between these two groups.

ZAKI. The Phase IV research area is a big melting pot for multiple disciplines — marketing, regulatory affairs, clinical research, data management, technology. We have to bring together people from a number of disciplines and, oftentimes, these people see the world in very different ways. It is always interesting to put them together in one room to try to solve a unique problem. This is not an area for the inexperienced.

MASSEY. Balancing the needs of all the stakeholders in Phase IV trials — marketing, clinical, patients, as well as healthcare practitioners — and ending up with data that improves a product's utility is a challenge, but it is also the goal of a successful product plan. Phase IV studies have the potential to improve patient care and product satisfaction, and both of these factors optimize appropriate product use.

BRADSTREET. One of the major challenges facing the designers of Phase IV clinical trials today is finding the correct balance between risk management — for example, collecting safety and outcomes data — from a large patient population, and marketing support for a newly launched drug. The main purpose of Phase IV studies, even when carried out voluntarily without a FDA mandate, is risk management. Marketing support is an added value that and, while legitimate in and of itself, should not play a pervasive role in study design.

GUSELLI. Patient-experience programs are expected to be part of a new emerging area of risk management for pharmaceutical companies. As the FDA continues to push mandates and guidances for better structured risk-management programs associated with drugs in the commercial marketplace, the monitoring of patient populations on particular drugs will be necessary.

GLIKLICH. The first thing to realize when designing a Phase IV trial is that the goals are different from preapproval trials, the investigative sites are different, and the message should be different. Most Phase IV trials try to demonstrate that the results stemming from clinical trials under very controlled circumstances are true when the drug is in the real world. To do this requires a representative group of patients and a representative group of trial sites. One of

Summary of Postmarketing Study Commitments to CBER and CDER

(Numbers as of September 30, 2002)

Applicants with open postmarketing commitments

NDA and ANDAs = 126 BLAs = 44

Number of open postmarketing commitments

NDA and ANDAs = 1,339 BLAs = 223

	NDA ANDAs	% of total	BLAs	% of total
Status of open postmarketing commitments				
Pending	820	(61%)	67	(30%)
Ongoing	285	(21%)	102	(46%)
Delayed	25	(2%)	17	(8%)
Terminated	8	(1%)	2	(1%)
Submitted	201	(15%)	35	(16%)

Concluded studies

NDA and ANDAs = 349 BLAs = 52

	NDA ANDAs	% of total	BLAs	% of total
Commitment met	240	(69%)	47	(90%)
Commitment not met	0	(0%)	1	(2%)
Study no longer needed or feasible	109	(31%)	4	(8%)
Open postmarketing commitments with annual report due but not received	289	(22%)	77	(35%)

Source: Department of Health and Human Services, Food and Drug Administration, Washington, D.C.: Federal Register, May 21, 2003, Vol. 68, No. 98 — Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Commitment Studies: Availability.
For more information, visit fda.gov.

the big differences between a Phase IV trial and a preapproval trial is that Phase IV trials require a scale up to include hundreds of sites and thousands of patients as opposed to a few sites and tens or hundreds of patients. Scale is critical.

KRAPF. Patient recruitment and investigative site start-up are among the key challenges facing Phase IV trials. Typically these trials are marketing driven and need to incorporate a large number of patients in a short amount of time. In addition, the budgets associated with Phase IV trials tend to be low, leaving little room for inefficiencies at the investigative sites. Sites need to find the patients, qualify them, and get them through the trial as expeditiously as possible. The pharmaceutical sponsor is often anxious to get the results as quickly as possible to make marketing decisions to take the drug into new applications.

GUSELLI. Patient-experience programs provide new information about the performance of the drug to the medical community as well as the pharmaceutical manufacturer, and we eliminate the complexities of clinical-trial recruitment and IRB oversight. We don't recruit patients for a clinical trial, we are not doing randomization studies. These programs are designed to be interactions between physicians and patients in real-world practice settings. We are facilitating communication between patient and physician.

Creating Higher Standards

RUFFOLO. At Wyeth, we are restructuring our organization to pull all studies under one roof. So when we do postmarketing studies they are done to the same high standard as other clinical studies. In the long run, we will generate better data. Even if we conduct fewer studies, those conducted will be better and more relevant.

CLAGHORN. Marketing needs to be educated on the appropriate design of Phase IV studies. In essence, marketers need to know that they can't pay physicians to use their drug. Also, the American Medical Association needs to encourage physicians to more closely scrutinize the studies they agree to do.

MASSEY. Institutional review boards are critical for protecting patient safety. There is a need for better instruction and guidance to IRBs on how to appropriately assess the design validity of comparative studies. Optimal design of Phase IV studies, and any other clinical study, places patients' welfare first and tests meaningful clinical and scientific hypotheses that further the knowledge of a drug's effects.

O'CONNELL. Having standards in place, such as a set of clear best-practice guidelines for Phase IV trials, is a good idea. Such guidelines could provide a more solid context, and Phase IV trials could be evaluated in such a frame-

work, for example to determine whether they are flawed with respect to a particular guideline.

STUDIES THAT WILL FURTHER THE SCIENTIFIC KNOWLEDGE AND ENHANCE THE MEDICAL VALUE OF A PRODUCT CAN BE USED IN MARKETING AND PROMOTION EXTREMELY WELL. This should be the ultimate goal of Phase IV trials. Both criteria can be met very effectively.

CLAGHORN. The Pharmaceutical Research and Manufacturers of America (PhRMA) did a very good job of curtailing the money spent by sales reps on physicians in doctors' offices. It would be good if PhRMA, maybe in concert with the American Medical Association, came up with a set of self-policing guidelines for Phase IV studies.

RUFFOLO. I am all for self-policing until we find it doesn't work. I do worry about more regulations coming from the FDA, EMEA, and Japanese regulatory agencies, especially regulations that could have a significant impact on clinical development. If PhRMA, or a similar organization, was to come out with guidelines, that would be fine as long as the industry had input. I prefer self-policing until it is determined that this is not working.

BRADSTREET. Guidelines can be a good thing, as long as they are carefully thought out. The question becomes who would create the guidelines and who would critique them? This may not be necessary since the FDA already regulates sponsors and researchers, and physicians have their code of ethics to rely on, which is applicable to all areas of their practice, including Phase IV studies.

KRAPF. The range of Phase IV studies is such that a standard design of one-size-fits-all may mean that one-size-fits-no one. There are a number of approaches to enhance Phase IV trial conduct, such as using electronic data capture with predefined electronic case report forms, which can accelerate each aspect of a Phase IV trial from patient recruitment through database lock. Combining this with an Internet portal to share information among investigators, sponsors, sites, central labs, contract research organizations, and site management organizations can add another level of standardization to the trials.

WHITE. There are so many therapeutic areas and so many different issues associated with each that putting in place study-design stan-



HANI ZAKI



DR. JEFF WHITE

Too much marketing influence could instill bias in the research study design, but this should be apparent to a well-trained reviewer. **MARKETERS SHOULD BE INVOLVED, BUT NOT TO THE DEGREE THAT THEIR INPUT IS INFLUENCING THE STUDY DESIGN.**

PATRICIA BRADSTREET



PHYSICIAN PARTICIPATION IN PHASE IV TRIALS HELPS TO ENSURE THAT ADDITIONAL MEDICAL INFORMATION IS GENERATED,

allowing physicians to make better-informed choices in their prescribing decisions.

C. DAVID CLAGHORN



It would be good for PhRMA, maybe in concert with American Medical Association, to **COME UP WITH A SET OF SELF-POLICING GUIDELINES FOR PHASE IV STUDIES.**

dards would be difficult. But there are certain standards that should be in place. Phase IV studies should be compliant with FDA regulations, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) stan-

dards, and other generally accepted guidelines for good clinical practice. ♦

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

FDA-requested Phase IV Studies: Addressing the Burden of Postmarketing Commitments

The Food and Drug Administration announced in May 2003 measures to inform the public about the status of manufacturers' commitments to carry out postmarketing studies following the FDA's approval of certain drugs and biological products.

One of the measures was the publication of the FDA's first annual Federal Register report on postmarketing studies, which covers commitments that are required by the FDA as well as those voluntarily accepted by the manufacturers.

The FDA requires postmarketing studies for all products that receive accelerated approval; these are products that provide meaningful therapeutic benefit for patients with serious or life-threatening diseases for which there is no other available therapy.

The regulatory agency may also request a postmarketing study to develop information that, although not essential for approval, is important for improving the use of the product, product quality, or consistency in product manufacturing. These voluntary commitments are agreed to in writing by the applicants.

It is these voluntary commitments that are becoming a burden to the industry at an alarming rate, according to Robert R. Ruffolo, Ph.D., president of research and development of Wyeth Pharmaceuticals, and senior VP of Wyeth.

"Requests for additional studies postmarketing have become nearly automatic," he says. "These studies account for 26% of funding allotted for all preapproval and postmarketing clinical studies, which is money that becomes unavailable for funding the development of innovative new drugs.

"This contributes to the decrease in productivity that has become so apparent," he

says. "A good amount of our resources are diverted away from new drugs to study drugs that have already been determined to be safe and effective."

According to the Food and Drug Administration, more than 60% of the 1,339 promised postmarketing studies for pharmaceuticals have not begun and about 30% of the 223 promised studies of biological therapies have not begun.

According to Dr. Ruffolo, oftentimes regulatory agencies, including the FDA, EMEA, and Japanese authorities make postmarketing studies a condition of approval.

"After a company has spent 15 years getting a drug through development and on the market, it has to accept these studies in exchange for the approval," he says. "The approval, which a company has been waiting for many years, may be held over its head in exchange for agreeing to do a study that it doesn't want to do."

If a pharmaceutical company does not fulfill a postmarketing commitment, the FDA can pull the drug off the market.

Dr. Ruffolo believes to overcome this disconnect with the FDA, companies need to have discussions with regulators much earlier in the process about the need for postmarketing studies.

"I'd like to engage in a dialogue earlier with the agency, not at the last minute when an approval is being held under the condition of doing another study," he says.

Dr. Ruffolo says, however, that in cases where regulatory agencies grant accelerated approval, based on limited data, postmarketing studies are not a burden and should be undertaken.

"Of course companies should do postmarketing studies in these instances," he says. "This should be the exception but it's becoming the rule."