

No Fazing Phase I Growth

Phase I studies have become more complex as drug sponsors want critical data about their compounds to help inform decision-making and avoid expensive late-phase failures.

For CROs that offer early phase services, the future looks good. Demand for outsourced phase I work is increasing at a 13% to 15% rate, slightly higher than the 12% growth rate reported last year.

Many drug sponsors—under pressure to develop new drugs quickly and at the lowest possible cost—have focused on phase I in an effort to get more information about their drug candidates in a shorter period of time.

Phase I studies have become more complex, ask more questions and add patient volunteers earlier than in the past as drug sponsors want critical data about their compounds to help inform decision-making and to potentially avoid an expensive late-phase failure.

CROs have continued to strengthen their service offerings and capacity to meet the growing demand in the phase I marketplace. While merger and acquisition activity in phase I has slowed during the past 18 months, capacity has grown significantly as CROs have opened new phase I facilities and expanded the number of beds in existing units. At the same time, global CROs have publicized strategic plans that include strengthening early phase services overseas.

For CROs that offer early phase services, the future looks strong. Biotechnology companies, which often lack infrastructure and rely on CROs for development of early phase products, have been touted as providing a growing percentage of the drug development pipeline. At the same time, pharmaceutical companies, some of which have closed their own clinical research units in order to reduce fixed overhead costs and improve efficiency,

have increased the amount of work outsourced to CROs, a trend analysts expect will continue. “It’s a very exciting space. It has a lot of potential and it’s growing very robustly,” said Mary Westrick, Ph.D., global vice president and general manager of Clinical Pharmacology at Covance.

Demand Continues to Grow

Some larger CROs reported even higher growth than the 13% to 15% estimated by industry analysts. Quintiles, which tripled its bed numbers in the U.S. earlier this year, reports that its phase I business is growing in excess of 30%. Kendle executives estimated that the phase I market will grow between 13.4% and 16% annually through 2010 and that phase I growth will outpace the broader outsourcing market.

These strong growth numbers refer specifically to phase I studies that bring novel compounds into the first-in-man and proof-of-concept space as opposed to bioequivalence work, which is also labeled phase I but has different dynamics in terms of operations and costing. Some CRO executives see a slow-down in the bioequivalence market and report that the demand for phase I services from pharmaceutical and biotechnology companies is running ahead of demand from generic clients.

During the past 18 months, early-phase business has benefited from growth in pharma R & D spending. According to figures released by Goldman Sachs, phase I R&D spend in the U.S. was \$5.2 billion in 2005 and is projected to grow to \$8.9 billion in 2010. In addition, the outsourced phase I market has seen gains due to the number of new drug candidates entering clinical testing. In 2007, more than 250 drugs entered phase I trials. “They are making better decisions in preclinical, so more compounds are coming through to us,” said Covance’s Westrick.

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PHASE I

continued from page 1

outsourced phase I programs are difficult to determine, yet industry experts estimate the percentage of phase I work outsourced to CROs to be somewhere between 25% and 50% of the market. When it comes to the generic industry, about 95% of the phase I studies are outsourced. While in recent years a few of the larger pharmaceutical companies have added phase I facilities, including Pfizer and AstraZeneca, the stronger trend has been for pharmaceutical companies to close their clinical research units as a way to decrease their fixed overhead, gain flexibility in cost structures and improve efficiency. In the most recent example, when Eli Lilly announced it was selling a major R&D facility in Indiana to Covance, the pharmaceutical company also indicated its phase I unit in Indianapolis will probably close since the facility's workload will be substantially reduced.

"For pharmaceutical companies, the actual pipeline isn't always a smooth pipeline, so you may have a number of compounds coming through at a particular time that would justify having your own phase I unit, but if you don't have compounds coming through, that is a lot of fixed overhead to keep when you don't have anything to feed it," said Eddie Caffrey, senior vice president, Global Phase I, at Quintiles. "This variation in the pipeline has led sponsors to think that there are lots of good providers out there and this is something we can have off our books and just use the resource when we need it, as opposed to having it as a fixed cost."

In addition, biotechnology companies comprise about 30% of the total clinical development outsourcing market, a figure many analysts expect will increase to 50%

during the next couple of years. And for biotechs, which often lack internal development capabilities, a successful phase I study represents the chance to improve valuation of the new molecular entity (NME) and obtain funding from investors; for those developing new compounds with the intention of selling them to big pharma, the first-in-man and proof-of-concept studies are critical requirements for licensing deals. "This will continue to be a robust area," said Philip J.W. Davies, vice president, Early Stage, Kendle.

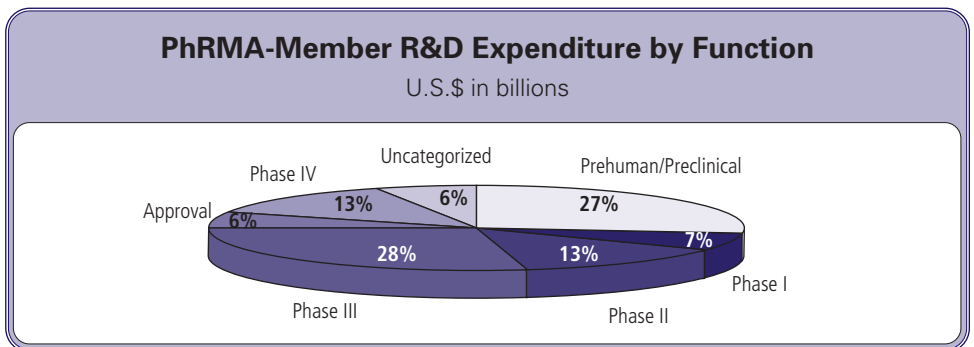
CROS Adding Capacity

The phase I market saw some consolidation about two years ago when many leading CROs bought phase I units, particularly in the United States. That flurry of mergers and acquisitions in the space has slowed, yet there were still several significant acquisitions in the phase I space during the past 18 months. In October 2007, PRA International acquired Pharmacon, a CRO that specializes in conducting phase I studies with patients in several Central European countries. In another deal worth upward of \$24 million, Kendle boosted its early stage capabilities in June with the acquisition of DecisionLine, a central nervous system (CNS)-focused phase I company located in Toronto. DecisionLine, formerly Ventana Clinical Research, operates an 82-bed facility in downtown Toronto and

has a staff of about 240 scientists, nurses and clinical development personnel. Four months earlier, Ireland's ICON bought a phase I unit in the United States with the acquisition of Healthcare Discoveries, which operates an 85-bed clinical pharmacology unit in San Antonio, Texas. Also in February, QPS, an early-phase CRO based in Delaware, acquired Bio-Kinetic Clinical Applications, another early-phase CRO with a 240-bed phase I facility.

During the next 12 to 18 months, David H. Windley, CFA, CPA, managing director of Healthcare Equity Research at Jefferies & Company, sees the possibility of more acquisitions in the phase I space. "Perhaps it will be via divestiture from pharma," he said.

Most of the phase I CRO activity during the past 18 months, however, has focused on adding capacity. Quintiles, for example, recently opened a new 150-bed phase I clinical research unit in Kansas, tripling the capacity of its former phase I unit that had been located in a nearby community, and is looking to expand its overseas facilities, which now include units in London and Sweden. PRA International also expanded its phase I capabilities with the opening of a new clinical pharmacology facility in Kansas in February. The \$2-million expansion doubled the capacity of PRA's existing clinical pharmacology center in the region to 80 beds. In addition, at the

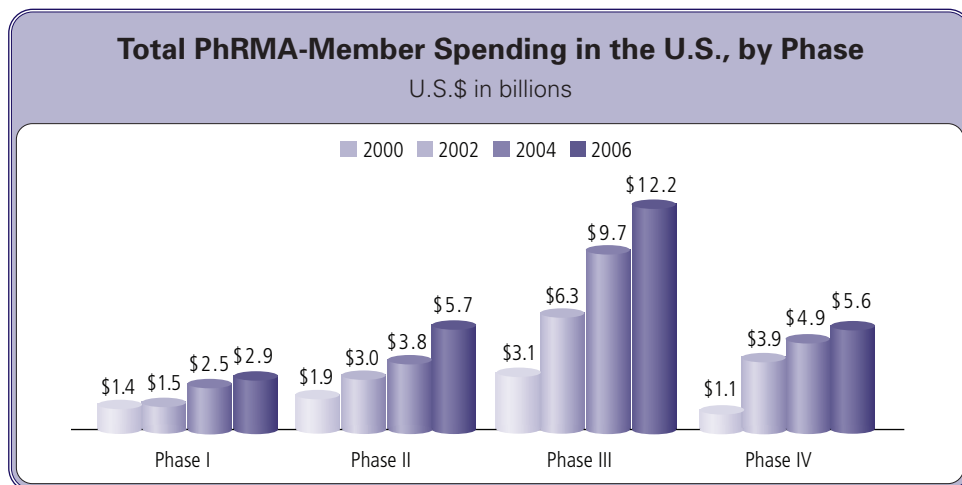


Source: PhRMA Industry Profile, 2008.

end of January, MDS Pharma Services opened a new 300-bed phase I clinic in Arizona. The \$25 million facility more than doubles the capacity of the CRO's phase I presence in Arizona, which, combined with a nearby existing unit, totals 420 beds.

Global CROs also are strengthening their service offerings and phase I capacity both in the United States and overseas. Parexel recently boosted its clinical pharmacology capacity with the completion of phase I expansions in three global locations: A unit in Baltimore, Md., has been expanded to 90 beds; the London site has been expanded to 64 beds; and two Berlin research units now have 160 total beds. In addition, PRA relocated its existing German operations into a Berlin-based facility that triples the size of its existing site; the new location was needed to accommodate increased early-phase staff from PRA's acquisition of Pharmacon. "The demand for phase I patient studies is growing exceptionally fast," said John Horkulak, PRA's vice president of Early Development Services, Central and Eastern Europe. "The expanded offices in Berlin, from where we coordinate our trials in Central Europe, are designed to support this fast growing business."

This trend toward expanding capacity of phase I beds, both in the United States and overseas, has not been limited to large CROs. Smaller organizations also are responding to the growing demand for phase I services. For example, Reston, Wash.-based Rainier Clinical Research Center (RCRC) expanded its early stage operations with the launch of a large phase I specialty unit within its existing facility; the center created the unit to help RCRC bring in the special patient populations that sponsors now want in early stage research. The phase I unit has six in-patient beds for overnight



Source: PhRMA Industry Profile, 2008.

studies along with outpatient care capabilities.

In another example, Overland Park, Kan.-based clinical services company Vince and Associates Clinical Research opened a new 16,000-square-foot, 50-bed phase I trials facility in June. While the company previously specialized in phase II and III trials, Vince and Associates established its first phase I facility after drug sponsors consistently asked the company to participate in phase I outpatient studies. "We've seen such an increase in demand from pharmaceutical companies wanting our services on the phase I side. So we went ahead and built out an entirely new unit to keep up with client's requests," said Brad Vince, M.D., the company's founder and CEO.

More Complex Studies

In recent years, phase I studies have become increasingly complex, the protocols ask a greater number of questions, and studies more commonly include intent-to-treat patients as drug sponsors want to understand not only the benefits, but the liabilities of their compounds more quickly.

Pharmaceutical companies, which find themselves under tremendous financial pressure in the face of patent expirations for

top-selling medicines, want to find winning molecules as early in the development timeline as possible. "Because of the huge investments that have to be made, both the manufacturing of active pharmaceutical ingredients (API) and final formulations as well as the larger trials that go into phase III, these investment decisions are increasingly triggered off a series of carefully designed, complex studies that we actually design and execute in this early phase space," said Kendle's Davies. "These studies now produce enough data to really help predict the possibility of a technical and commercial success of those drug candidates—I call them drug candidates because they are unproven at that point. But the goal here, and the aim of the industry, is to find the winners earlier and have the critical data available to drive the decision-making."

CROs report that sponsor companies now require multiple studies on the same compound in phase I and want to answer more questions about the drug before moving onto phase IIa. "Instead of the individual studies that we used to see in the past, where you do a single ascending dose study and a multiple ascending dose study—your SAD study and your MAD study—now they are being combined. And they might

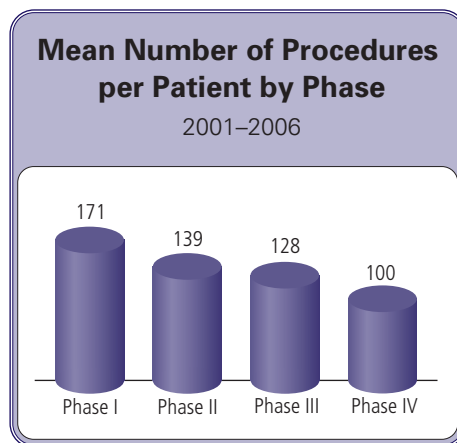
see PHASE I on page 4

PHASE I

continued from page 3

have a couple of other arms on it as well. And we are seeing first-in-human packages that combine about four different kinds of studies and endpoints. That is becoming more and more common,” said Covance’s Westrick. “Our clients are under a lot of pressure to go more rapidly. This is a way to get more information in a shorter period of time. The safety is still built in, but there are some things that they used to do sequentially that they can overlap to some extent now. You always could overlap these studies, but it was that people didn’t want to because if your drug tanks on a single ascending dose, you don’t want to spend any money on the multiple ascending dose study. Now it’s a trade-off between time and money and the additional investment in making a larger protocol. An umbrella protocol that would encompass the multiple dose study and being able to gate that in the appropriate time after the single dose study is minimal when you look at the amount of time that you are held up assuming your single dose study is successful.”

Similar trends have been seen across the industry. At Rainier Clinical Research, for



Source: CenterWatch analysis, 2008; Fast Track Systems, 2007.

example, Leslie Klaff, M.D., Ph.D., one of the center’s founders, said that requests for intent-to-treat type studies are becoming more and more popular at his center. “These are the half phase I-half phase II scenarios, where you do some initial phase I studies in patients, send them out for two weeks on the drug, and then bring them back in for additional phase II-like testing,” Klaff said.

Including patient volunteers in phase I trials can allow drug sponsors to learn more about the potential of their compound in a shorter amount of time. “There is only so much in terms of efficacy that you can show in healthy volunteers. We may be able to get some biomarker evidence that a compound

has some efficacy. But you really need to get into the patient population to really have proof of concept,” said Quintiles’ Caffrey. “Another trend we have seen based on the complexity of the molecules, when you get into things like monoclonal antibodies, is that the regulatory authorities actually insist that instead of going into healthy volunteers with some of these compounds, you really need to be going into the target patient population for the first-in-man.”

While drug sponsors have added patients to early phase studies for more than a decade, the way patients are incorporated and the objective of their involvement has changed in recent years. “It’s really not to prove efficacy in the way that a large phase III or even a phase II trial would. It’s more to understand the pharmacology and the action of the molecule. We study patients a lot sooner into this phase than previously and that is also driven by the desire to better understand the mechanics of the disease, the progression of the disease, and to build disease-state models, which are mathematical models, which help predict outcomes. Including patients in the early trials is important to explore indicators of response; biomarkers are utilized to look at a biologi-

Estimated Revenues of Select Public CROs

Percentage of revenue by phase and function

Company	Preclinical	Phase I	Phase IIa	Phase IIb	Phase III	Phase IIIb-IV	Central Lab	Bioanalytical	Other
Charles River Labs	50%	3%							47%
Covance	29%	4%		18%		8%	28%	9%	4%
ICON			5%		60%	20%	10%		5%
Kendle	2%	10%		70%		14%			4%
Parexel		14%		50%		16%			20%
PPD	1%	4%		55%		20%		16%	4%
PRA		5%		87%		8%			
PharmaNet		15%		54%		6%		25%	

Source: Jefferies & Company, Inc., 2006.

cal response and compare and contrast the level of signaling in a patient population compared to the responses in healthy volunteers. Patients are important. They are important to understand the potential of the molecule, as well as the potential of the targets that the drug companies are going after,” said Kendle’s Davies. “In fact, I’m seeing a trend that patients may be involved in trials right off the bat—so patients would be exposed to drugs at the very start of the true first-in-man trial.”

Rather than adding a patient arm onto an existing protocol, drug sponsors have begun to plan the inclusion of intent-to-treat patients in phase I trials upfront as a way to avoid gaps between the end of a phase I study and the start of a phase II study in patients. At Parexel, its early phase services division, Parexel Clinpharm, helps sponsors make strategic decisions early in development about questions such as whether to add patients in phase I. “Traditionally, Parexel’s phase I work focused on healthy volunteers, but we are moving more toward early drug development, which includes proof-of-concept work. We are seeing, across the board, that sponsors are seeking patient volunteers as soon as possible in phase I. We review every potential protocol we receive from a scientific point of view and suggest to sponsors, if it is necessary, different study designs,” said Michelle Middle, vice president and worldwide head of Parexel’s clinical pharmacology business. “We are heavily involved in bridging studies, where you have both healthy and patient volunteers in one protocol. It is critical not to extend set timelines. You have to have a very effective system.”

Phase I studies also have become more complex through the use of advanced technologies, such as molecular imaging and

new imaging techniques, that can speed up the development process and give drug sponsors more information about their compound. At Covance, for example, clients increasingly use tiny radio labels, which are smaller than standard radio labels, with a therapeutic dose of the drug in phase I trials. “Clients are trying to get much more information up front than they ever have before,” said Covance’s Westrick. “We are seeing some of these trials that we’ve never seen in this type of paradigm. Clients want a SAD study, overlaid with a MAD study, overlaid with a food effect, overlaid with a probe—that seems to be a standard package now.”

New Challenges for CROs

The growing trend of enrolling patient volunteers in phase I studies creates new challenges for the CROs running these trials.

First of all, CROs need to find the patients to enroll in these phase I studies. “Most traditional phase I units have a great database of healthy volunteers. However, trying to recruit patients for a study that has very little chance of helping their medical condition makes recruitment challenging,” said Covance’s Westrick. “Even if the drug works and ends up being the greatest thing since sliced bread, they are not going to be on it very long. And it’s not like a phase III protocol where they are going to have the option to continue on the drug when the study is over. It’s going to be a very short period of time on the drug and typically it’s not even going to be long enough to see a lot of therapeutic benefit unless you’ve got a really robust biomarker. Trying to recruit a patient by saying, ‘We’d really like you to participate in this trial with a new drug, we believe it’s got a lot of promise, but it’s really not going to help you right now,’ is a little bit difficult.”

In addition, the industry is still finding its feet in terms of how to plan for patient accruals in phase I, Kendle’s Davies said. “Traditional early phase studies are performed, or were performed, in a cohort approach where maybe eight or 12 subjects would be studied all on the same day in the same clinic under identical conditions, under very controlled conditions of diet, exercise, activity, dosing times. It was very, very regimented to reduce variability. The early expectation was that the patient accruals could happen in a very similar fashion,” he said. “The experience is showing that patients really are not as accessible due to a whole range of reasons, including stringent inclusion/exclusion criteria, especially around co-medication. It’s not possible to do these trials, by and large, in groups of 12 or 15 subjects all in one day. So they tend to be individual or just a couple of subjects at a time. That adds on to the overall length of a particular trial, which is counter to the demands on the industry. One way to mitigate this is by opening more sites in the phase I environment—five, six or seven sites—to try to deliver three or four subjects at each site and keep on track. So there is a complexity factor to that as well.”

Looking Ahead

Last year, the U.S. Food and Drug Administration (FDA) saw a jump in the number of investigational new drug (IND) applications based on data gathered from early-phase research conducted outside of the United States. The agency reported a trend for INDs “to be opened with studies of increasing complexity, such as late phase II or III clinical trials that are intended to be part of an NDA or BLA submission, or phase II trials that will affect the design of subsequent pivotal trial protocols, after

see PHASE I on page 6

PHASE I

continued from page 5

completion of early phase clinical trials in non-U.S. sites.” While the FDA didn’t offer specific figures or explanations for the trend, which was noted in a manual of policies and procedures released by the FDA’s Center for Drug Evaluation and Research (CDER) last year, the observation shows a growing tendency for drug sponsors to conduct early phase work in accredited sites outside of the U.S., then obtain an IND using preclinical, phase I and phase II data from those studies.

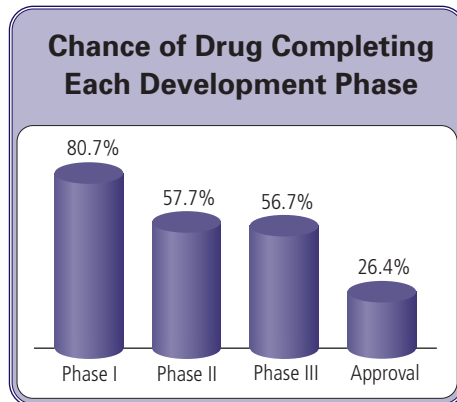
At the moment, global CROs report drug sponsors are mainly interested in placing their complex phase I studies in Western Europe and North America; in fact, a Goldman Sachs report found that about 76% of the phase I work in 2007 was conducted in the United States, Canada and The Netherlands. “It comes down to total infrastructure, as well as the medical competencies and proven pedigrees of investigators because in phase I, the CRO clinics are in the unique

position where they are both the site and the investigator. The physicians are generally employed by the CROs. The ability to deliver high-class clinical pharmacologists and other well-trained medics who have a pedigree in drug research as well as medicine is very, very important. I think we will continue to see the more novel, sophisticated complex studies predominately play out in North America and Western Europe,” said Kendle’s Davies.

In future years, as capabilities for phase I

studies increase in emerging markets, some industry analysts predict that many of the more straightforward studies, such as the routine bioequivalence studies that have traditionally been done in the United States, may go overseas purely for cost considerations, while more complex studies that require an established innovative base of clinical pharmacology expertise will remain in North America and Europe. “Looking out over the next 18 months, I see a pretty robust market in the U.S.,” said Quintiles’ Caffrey. “I also see an interest in other overseas markets, in particular the experienced, well-run units in overseas markets. While sponsors tend to outsource simpler, straightforward studies abroad and keep their more complex ones at home, whether that be in the United States or Europe, as other markets develop, we will see the emergence of more experienced units in overseas markets.”

—Karyn Korieth



Source: RA Abrontes-Metz, et al., FTC Bureau of Economics, Oct. 2004.