

A Prescription for R&D Refills

PHARMACEUTICAL AND BIOTECHNOLOGY DRUG DEVELOPERS

APPEAR TO BE MAKING SOME PROGRESS IN THEIR PERENNIAL QUEST

to bring more and better products to market with greater speed and efficiency.

by
Carolyn Gretton

The clinical development sector still faces a rough ride in the short term as it scrambles to replenish portfolios flattened by the continuing avalanche of patent expirations for products ranging from mass-market blockbuster drugs to medicines targeted at highly defined populations.

According to the Outlook 2010 report from the Tufts Center for the Study of Drug Development (CSDD), worldwide sales for all drugs coming off patent from 2009 through 2012 will exceed \$88 billion. Drug developers and the U.S. Food and Drug Administration have worked hard to speed up the drug-development process; total average clinical time dropped by 10% from 1992 through 2007, even as trials became more complex, while average approval times declined by nearly 60%. Despite these improvements, it still takes an average of more than \$1 billion and more than seven years from the start of clinical trials to conduct the necessary studies and win approval to market a new drug in the United States, the report found.

"The simple fact is that product launches are not keeping pace with patent expirations," says Tufts CSDD Director Kenneth Kaitin. "Developers have made important progress in reducing R&D times, but because only three in 10 new drugs, on

average, generate sufficient revenue to sustain R&D, pharmaceutical and biotech firms are under great and growing pressure to generate revenue to bring more products to market."

Tufts CSDD research does suggest that sponsors are becoming more aggressive in terminating unpromising drug candidates, enabling companies to redirect their R&D resources to other projects that show more potential. Factors helping to drive this change include the growing use of forward-looking development metrics that link operational goals with company business objectives, greater emphasis on team participation in individual performance reviews, and the forging of more collaborative relationships with outside service providers.

Douglas Winship, VP of regulatory operations at Catalyst Pharmaceutical Partners, says he perceives the clinical development process as moving toward a scaling-back of the data collected in trials, focusing only on those data needed to demon-

strate safety and efficacy for the indication being studied.

"I think that takes more time up front to model anticipated response rates needed to achieve statistical significance," Mr. Winship says. "Since the cost in time and money of a failed trial can never really be made up, it is incumbent to learn all one can from the experience, so that chances of the next one succeeding are maximized. Unfortunately, it is by no means a given these days that a second opportunity will be given."

Nathaniel Brown, M.D., chief medical officer and senior VP, clinical development, at Presidio Pharmaceuticals, cites continuing improvements and standardization in IT and data management processes as recent developments contributing to improved efficiencies in clinical operations.

"These improvements are reducing concerns about dataset incompatibilities, and are minimizing compliance issues with the evolving regulatory

THOUGHT LEADERS

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Dr. Jeffrey Kasher

Lilly

The fundamental differences in the business models of CROs and pharma companies like Lilly

make it difficult for CROs to truly shoulder an equal share of investment or risk in developing a drug candidate.

centers engaged in trials. Beyond classic laboratory tests, medical images are raw datasets that empower the industry to improve imaging software or revisit previous trials with new technologies in efforts to discover new information. (For more information, please turn to page 16.)

Maria Smith, global head, operations — affiliate management, product development, for Roche, says her company has been working to identify how it can apply more of a “fit-for-purpose” approach to ensure effective use of resources, while maintaining data quality and ensuring continued patient safety.

“From a monitoring perspective, this means looking at the activities that can be done as or more effectively remotely versus requiring an on-site visit,” Ms. Smith says.

At Lilly, Jeffrey Kasher, Ph.D., VP for global clinical

development, says all clinical development work is exclusively reported via EDC, which has improved quality and speed of data collection and reduced the associated costs.

“We’ve also worked to improve training for internal personnel and CROs that interface with our clinical trial sites to ensure that these individuals continue to improve their regulatory knowledge, as well as their knowledge of particular molecules and disease states,” Dr. Kasher says. “And we’re improving the quality of training we provide for individual study sites to ensure we’re giving these experienced individuals the information they need to appropriately recruit and conduct trials.”

Sites and investigators are two of the most prevalent bottlenecks in clinical development, and according to Bill Gwinn, VP, clinical informatics solutions, at i3 Pharma Informatics, the investigators with the most matching patients will naturally have an easier time recruiting. The most powerful predictor of success is the patient count by site or investigator. Insurance claims can count specific patients, only those who match all of the inclusion and exclusion criteria. Being specific is important in finding investigators with rare patients. (For more information, please turn to page 12.)

UPGRADING CRO CONNECTIONS

While new technologies and improved protocol designs are helping to improve R&D efficiency, future success for many drug sponsors will depend on their ability to collaborate with other drug companies, and how well they engage and partner with outside service providers, Mr. Kaitin says. According to Tufts CSDD’s Outlook 2010, while global spending on new drug development has been growing at an annual rate of 9.1% during the past decade, spending on contract clinical services has been growing almost 50% faster — at an annual rate of 13.4%. Even as the number of companies with active clinical projects worldwide increased by 80% between 2000 and 2008, sponsors have maintained stable R&D headcounts by working with CROs. Tufts CSDD expects the trend to work even closer to improve R&D efficiency to continue, as both parties develop ongoing alliances in place of traditional transactional relationships.

A recent white paper from INC Research con-

requirements toward electronic submissions,” he says.

According to Jon DeVries, president of Merge Healthcare’s eclinical division, imaging is increasingly being viewed as one of the most powerful cost-savings strategies to measure and monitor the effects of the drug or device under evaluation.

Concurrent and continuous advances in imaging technology have firmly established imaging devices in the clinical testing armamentarium of

R&D, Biotech Hit Hard by Downturn

Curbing costs in response to the global economic downturn, as well as the continuing capital crunch, is likely to have a long-term impact on the life-sciences industries, according to a survey by Deloitte in collaboration with The Economist Intelligence Unit.

Almost one-third of the executives surveyed see a reduction of R&D spend in the future, and nearly half believe that up to 40% of biotech companies will cease to exist in five years. In addition, almost one-third of respondents predict an outflow of scientists from smaller to larger companies.

Other findings:

- More than 65% of respondents indicated that their company has been moderately to significantly negatively affected by the recent global recession.
- A significant minority of 17% say the recession will cause major changes to their pre-recession strategy.
- Almost one-third of respondents specify that their company is reducing R&D spend and 43% indicate that their company is focusing on products with immediate returns.
- As capital market pressure eases, consolidation will likely pick up, with cross-border transactions accelerating and the largest companies will likely get bigger.
- With health plans’ increased focus on cost, the use of new tools like comparative effectiveness will most likely dramatically increase as companies are forced to justify the value of their products.
- The decline in R&D spending will likely have severe repercussions for the services sector. Nearly one-third of contract research organization (CRO) executives surveyed say the recession has had a major impact.
- With healthcare costs driving legislation that favors generic products, more companies are hedging their bets by acquiring generic product manufacturers.
- As growing, affluent markets in their own right, emerging markets are likely to become the life sciences battleground of the future, with 35% of survey respondents pointing to these regions as the most profitable geographic areas.

Source: Deloitte Touche Tohmatsu and The Economist Intelligence Unit.
For more information, visit deloitte.com or eiu.com.

firms this view, noting that drug companies can benefit from forging long-term alliances with CROs that encourage them to act as stewards of the companies' drug assets, and to share in the same incentives for the success of those assets through incentives such as milestone-based payments, risk sharing, or co-investment in assets. In the long-term, multidrug partnerships, CROs assume responsibility for complete testing of one or all compounds in the pipeline; management of a therapeutic area; or specific areas of the drug development process such as medical writing, data management, or biostatistics.

According to INC Research, these types of clinical delivery alliances can reduce costs by avoiding the start-up costs associated with project bidding and vendor management, as well as the costs associated with managing multiple vendors; and can minimize risk by shifting the sponsor-CRO business relationship to a performance-based alliance model with specific payment milestones, thus ensuring CROs have a financial stake in the trial's success.

Not all clinical development experts completely agree with this assessment, however.

"What INC presents can be true from a cost-savings perspective," Mr. Winship. "I note that I have always endeavored to negotiate a performance-based contract with specific payment milestones and I believe that works generally well. I would also note that the CRO's stake is in the trial's successful completion and meeting time goals in reaching completion. The risk of the actual trial success or failure generally remains with the corporate sponsors."

According to Dr. Kasher, the fundamental differences in the business models of CROs and pharma companies like Lilly make it difficult for CROs to truly shoulder an equal share of investment or risk in developing a drug candidate.

"There are some CROs that have investment arms, and one can engage with them as a potential partner that's looking to invest in the drug company's development, as well as potentially being the CRO that provides specific clinical services," he observes. "But in most cases, there can't be true risk-sharing or co-investment with a CRO beyond the small incentives and penalties related to the specific work the CRO is contracted to perform."

Lilly has ongoing relationships with several

CROs in areas such as clinical trial monitoring, and Dr. Kasher says this strategy has paid off in terms of quality and cost structure improvements.

"Both companies are contributing to the actual conduct of the trial in a way that is good for patients from a quality and safety standpoint, and that provides investigators with an interface with Lilly on all these trials," he says.

Dr. Brown does agree that preferred-provider relationships with CROs can benefit pharma/biotech companies through negotiated cost savings based on CRO discounts for continuing business, as well as time-and-effort synergies such as standardized data management and seamless safety monitoring through multiple stages of a given clinical development program. But he cautions, small pharma/biotech companies have different needs from larger firms that can prevent them from realizing the full advantages of such partnerships.

"Preferred-provider relationships work best for big pharma or mid-size pharma/biotech companies with substantial revenue and multiple Phase IIb-III-IV development projects," Dr. Brown explains. "For these companies, establishing long-term relationships with a large, multinational, full-service CRO can capture numerous efficiencies. But small pharma/biotech companies typically have relatively few clinical-stage projects and usually focus on Phase I-IIa clinical development, with a goal to outlicense their project or to form a development alliance for larger-scale Phase IIb, III, and IV trials. In this regard, the increasing availability of relatively small regional CROs, often with specialized therapeutic area experience and usually with lower overhead costs than the large CROs, can be an advantage for efficient conduct of Phase I-IIa proof-of-concept trials, especially for small companies."

By contrast, David Apelian, M.D., Ph.D., senior VP, research and development and chief medical officer for Globelmmune, says he thinks in some circumstances, a more robust clinical development alliance with a CRO could benefit smaller biotech companies.

"It's an interesting model where a CRO could contribute to the resources needed for a project in multiple forms, based on some of the services that they can provide, but also potentially on a financial investment and subsequent downstream expectation of value," Dr. Apelian says. "It's a good example

of how those relationships can mature into a more full-blown partnership, rather than simply a vendor-client relationship."

Simon Craw, Ph.D., VP, UniStemCell, at International Stem Cell Corporation (ISCO), believes the decision to partner with a CRO should be made on a case-by-case basis.

"Many CROs specialize in particular therapeutic areas and are therefore not suitable for broad relationships," Dr. Craw says. "On the other hand, small companies with limited budgets can find it an attractive way of sharing the development costs and associated risks."

Ms. Smith says Roche has developed strategic partnerships with certain CRO providers.

"We view this as a win-win situation, enabling us to work more effectively with them and providing the opportunity for knowledge sharing and development of best practices," she adds.

Because Presidio's projects are in early-stage clinical trials, Dr. Brown says the company currently outsources all data management to its midsized CRO partner:

"The past several years have seen increasing progress in improving hardware and software compatibility and in continuing standardization of clinical data management processes across various companies, vendors, and, to some extent, regulatory agencies," he observes. "An important practical benefit is there are fewer issues of electronic incompatibility for datasets collected for different trials in a clinical development program, even when the trials are conducted with different CRO/vendor support. Because of this, we can outsource our data management to one CRO with less anxiety about future dataset incompatibilities for different trials and stages in our clinical development programs."

The rigid user interfaces of legacy clinical trial applications are being replaced with SharePoint portals that present targeted information in a manner customized specifically for busy clinical trial managers, according to Bob Webber, VP, clinical trial management systems, at BioClinica.

"SharePoint has been adopted by more than 17,000 companies, and it has become Microsoft's fastest-growing server product ever," Mr. Webber says. "There is good reason for this exponential growth — people across diverse industries find that it improves productivity and takes the knowledge worker to a new level of real-time insight to



Dr. Nathan Brown

Presidio Pharmaceuticals

Preferred-provider relationships with CROs can benefit pharma/biotech companies through negotiated cost savings based on CRO discounts for continuing business, as well as time-and-effort synergies.

means that data are never entered into the computer more than once, simplifying quality control and providing data earlier in the process," he says. "The pervasiveness of global broadband Internet access, combined with significant investment by clinical trial software companies to integrate multi-lingual clinical trial data management systems and EDC systems has made electronic clinical trials much simpler for sites, investigators, and sponsors."

"Looking at the dramatic improvements in EDC system design, and how easy it is for users at the site and sponsor sides to navigate and utilize these systems, I think that has been a huge step forward in acceptance of EDC," Dr. Apelian says. "In EDC's early days, it took a lot more training to get site acceptance, and to get people to use them when they were supposed to. Not only are deployment and training a lot easier now, but the systems work better, faster, and more efficiently."

Some of the most significant trends in global trial costs are occurring in the area of reimbursement for completed patients/subjects. In the last five years, in Phase II and III studies, reimbursement has increased globally by 30%. France and Germany show the highest percent increase, at 50% and 41%

respectively. Conversely, compensation has decreased in South and Central America by 14%.

According to Lori Shields, VP, data operations, at Medidata, procedure costs, however, continue to fluctuate across the globe. A routine electrocardiogram typically hovers near \$107 in North America, while in South and Central America, it is reimbursed at \$71 and in Europe the rate drops to \$48. (For more information, please turn to page 14.)

TAILORING THE FUTURE

Most clinical development experts agree that cost management and efficiency improvements will remain two key challenges for clinical operations going forward. Dr. Craw predicts that companies may start turning to so-called "phase zero" and micro-dose early-stage trials as a way to gather enough data to make a go/no-go decision earlier in the development process. These trials involve administering minute quantities of a drug candidate to human patients prior to the initiation of Phase I drug-safety studies, and can help confirm bioavailability, pharmacodynamic, and metabolic endpoints earlier in the development

ViewPoint



Bob Webber
BioClinica

Many life-sciences companies are eager to benefit from SharePoint capabilities, but may be unsure how its capabilities can be leveraged in the highly regulated world of clinical trial management.



Bill Gwinn
i3

There are several ways to measure and describe investigators: location, experience, hospital affiliation, age and gender, foreign languages spoken, adverse actions, and specialty.



Lori Shields
Medidata

The overarching need to stay within budget remains, yet it will be important to be aware that the cost of executing clinical trials is definitely on the rise.



Jon DeVries
Merge Healthcare

Perceptions of imaging technology are changing — imaging is increasingly viewed as one of the most powerful cost-savings strategies to measure and monitor the effects of the drug or device under evaluation.

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process. However, Dr. Craw warns, these tests "obviously raise ethical concerns around dosing subjects with a drug without therapeutic intent, and possibly with more limited safety data than a traditional Phase I study."

Mr. Winship says companies will likely maintain their focus on implementing technology wherever possible to reduce costs.

"Companies can probably increase their use of more advanced EDC analytics to improve efficiency," Dr. Kasher adds. "We can also use technological tools to increase our centralized monitoring of clinical-data quality. We'll still need to have a human being visit the site and check the data, but if we could automate some of those processes, it would speed things up, improve overall quality, and help reduce associated costs."

Dr. Kasher also foresees greater utilization of adaptive clinical design, which can determine safety and efficacy with fewer patients by giving researchers the flexibility to make adjustments when a particular patient or dose group is showing inadequate efficacy or a higher rate of side effects.

According to Dr. Brown, the globalization of clinical development programs will continue to be an important driver of changes and improvements related to clinical operations.

"Appropriate globalization of clinical trial programs can lead to rapid, near-simultaneous registration in multiple global markets, with efficient availability of new medicines for needy patients worldwide, and with maximized global commercial returns during periods of patent protection for novel drugs," he says.

To address the challenges raised by this ongoing move toward clinical research globalization, Dr. Brown advises clinical operations executives to tailor their operational capabilities to meet the needs of diverse cultures and languages, and to negotiate registration goals with local regulatory bodies, which often maintain 'informal' clinical trial recruitment requirements despite increasing acceptance of ICH standards.

On the regulatory front, Mr. Winship says developers will likely continue to wrestle with the FDA in regard to pharmaceutical risk tolerance.

"The pendulum has appeared to swing to the safety side currently in approval decisions, leading to more and/or larger trials, which cost more and take more time," he says. "One consequence is loss of market exclusivity, shortening the time in which companies can recoup their investment and make an adequate return on capital based on the risk taken. This makes the industry risk perception in capital markets even higher, thus affecting the availability of risk capital to support additional development of new, life-saving therapies."

Another big challenge facing clinical developers, according to Ms. Smith, is making personalized healthcare a reality without further increasing the complexity of clinical trials. "One step to identifying solutions to these and other challenges is by supporting efforts such as the Clinical Trial Transformation Initiative, a public-private partnership which is an offshoot of the FDA Critical Path Initiative, aimed at modernizing how clinical trials are done," she observes.

Dr. Kasher agrees that pharma's future lies in



Douglas Winship

Catalyst Pharmaceutical
Partners

innovative medicines to treat medical conditions with unmet need. To that end, he recommends developers continue to embrace and focus on biomarkers and diagnostics.

"Those tools can be used to identify the right patients for trials, and to identify safe and efficacious medicines sooner in trials," he says. "They are essential to the development of tailored therapeutics, which is something that Lilly is really putting a premium on."

"I think you're going to see a lot more molecular medicine factoring into clinical design," Dr. Apelian predicts. "There's that whole fascinating aspect of how we can better preselect patients with certain genetic markers, or tumor markers in the case of cancer; and how that will help us to better understand how to treat those patients. I think it's a really incredible opportunity to improve how we customize and tailor therapies to the patients, and to give the patients with the best chance of response the best types of treatment regimens." ■

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