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CRO Outlook & Drug Development Trends

CRO industry grows as increasingly complex R&D trends demand advanced expertise

Among today's R&D trends, precision-based medicines and immunotherapies for smaller populations and treatments for rare diseases are driving innovation. Aside from the exorbitant costs tied to development, these treatments require advanced and integrated expertise. In an effort to contain costs and shorten development timelines, pharma and biopharma firms increasingly outsource many services associated with the development of today's complex therapies into the hands of CROs.

It's not just complex therapies, but also combination regimens, as well as delivery systems and companion diagnostics that require expert development strategies and protocols. Today, CROs need to be faster, smarter, and more responsive to accommodate these needs. Managing complexity continues to be a top priority for CROs.

The global CRO market, inclusive of early- and late-stage development services is forecasted to grow at a CAGR of 9.8% over the period 2014-2019, according to a recent report published by Infiniti Research Ltd. To calculate the market size, the report considers revenue generated from sales of outsourcing of R&D services to CROs by global pharma and biopharma companies. Drivers of this projected growth are increased R&D spend by biopharma companies, along with a growing pipeline of biologics for the treatment of diseases such as diabetes, cancer, and genetic diseases.

This article explores the trends that have shaped the drug development outsourcing market today and details the current and potential future opportunities today's complex therapies present. Also, executives from Pfizer, ACRO, Quintiles, PPD, Theorem, and more, share their efforts to streamline drug development within Sponsor/CRO partnerships.

DRUG DEVELOPMENT TRENDS

In light of the complexity current R&D trends entail, the de-

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mands on service providers have never been greater. The growth of the CRO industry overall implies it's meeting those demands. As seen in recent years, pharma companies are continuing to focus on cost containment and shortening development timelines without compromising quality. Payer pricing constraints, R&D budget constraints and the high cost for clinical development are forcing a consolidation of disease areas for drug development within pharma companies, according to Gautam Ranade, Ph.D., senior director of Strategic Sourcing at Pfizer Worldwide R&D. "These factors are driving increased business for CROs due to the potential flexibility offered by these arrangements. By the same token CROs need to align their service offerings for the pharma industry in light of these major trends and should also have the ability to support fast track regulatory pathways," he said.

John Lewis, senior vice president, Policy & Public Affairs at ACRO, noted, "We are continuing to see large pharma divesting parts of their R&D infrastructure, which bodes well for outsourcing in general. As a result, CROs are seeing annual growth in the range of approximately 10% in terms of revenues and employment. This also presents an opportunity for CROs to hire very skilled clinical researchers who have worked in the pharma industry. This was unheard of a few years ago. Now, according to the Tufts Center for the Study of Drug Development (CSDD), our members have more clinical research staff than the pharma industry. We have seen a real shift not only in terms of numbers but also in expertise and innovation."

The industry continues to be challenged by the rising cost of delivering new drugs to patients, and biopharma companies are reinventing themselves in this challenging research environment. Drug development takes too long and costs too much, according to Paul Colvin, executive vice president, Clinical Development, PPD. He noted several key trends impacting drug development today. "Predictive analytics and real-time data access are playing a major role in our initiative to bend the cost and time curve of drug development. Our technology platform, Preclarus, presents consolidated data on dashboards offering interactive visualizations and analytics aimed at enabling the earlier identification of issues and facilitating more informed strategies and more efficient operations." Bottom line, CROs must look at the entire life cycle of a study and find opportunities to reduce costs and speed time lines, while ensuring the highest possible quality. "This kind of sophistication and rigor in drug development is what biopharma clients are looking for," Mr. Colvin said.

Managing complexity is an essential objective for both sponsors and CROs alike. "Companion diagnostics, genomics and biomarker expertise will become a more critical part of the development process as companies require more customized and complex clinical trials," said Paula Brown Stafford, president, Clinical Development, Quintiles. Also, providing enhanced value for patients is a key focus, as regulations and legislation will increase the demand for innovative and cost-effective commercialization strategies, outcomes research and data analytics services. Another objective, according to Ms. Stafford is increased strategic collaborations, "Long-term strategic collaborations with global service providers will continue to provide biopharma companies the opportunity to utilize flexible business models and integrated end-to-end solutions to deliver on their strategic priorities."

More and more, the efforts of CROs and sponsors, pharma and biopharma alike, are intertwined, agreed Marc Hoffman, chief medical officer at Theorem. "The lines have continued to blur and the integration of efforts has grown seamless," he said. "As both disease diagnosis and treatments become more complex and we continue to recognize the promise of genomics and proteomics and more personalized medicine, clinical study designs themselves become more complex. The trend is for greater patient specificity and, in many cases, smaller studies. Finding the needle-in-a-haystack patient is less of the exception."

Also, today's therapies involve, not just larger molecules and immune-based therapies, but complex regimens and delivery systems as well. CROs need to be resourceful with their service offerings. According to Dr. Hoffman, "The trend toward combination products will continue to rise with drug/biologic/device or companion diagnostic and therapy combinations becoming the norm. CROs today must be smarter, faster and more agile, as it is no longer about brute strength. Additionally, companies are increasingly utilizing creative study design tools, such as adaptive design, which means the ability to gather and visualize data faster is essential to make smarter decisions sooner."

DEALING WITH COMPLEXITY

Within this R&D environment, immunotherapies, rare diseases, and personalized or precision-based medicine hold great potential for life saving medicines. For CROs, this translates into opportunities as well as presents a level of complexity impacting many functions of a CRO.

The field of immunotherapies is flourishing, driving innovation in today's R&D pipelines. Numerous pharma/biopharma firms have proven the value of these therapies in treating diseases and in particular, cancer. For example, Bristol-Myers Squibb's success with cancer treatment Yervoy, and most recently, the landmark first-in-class FDA approval and early efficacy data with its PD-1 therapy nivolumab. This drug unleashes the immune system to attack cancer cells, achieving complete or partial remissions in Hodgkin lymphoma patients with resistant forms of the disease. Also, Merck's pembrolizumab, initially approved in melanoma, is now expanding to other solid tumor indications.

"This type of research necessitates CROs be well versed in the safety, toxicity, and efficacy profiles of these cutting-edge therapies as they are significantly different from classic chemotherapies or even more modern biologics or targeted small molecules," said Andrew Zupnick, Ph.D., senior director, Oncology Division, Novella Clinical. "Additionally, CROs must be attuned to the unique logistics of drug manufacturing and handling, cold chain management, potential regulatory hurdles with a novel drug class, site capability needs such as IBC approvals for certain vaccines, global feasibility, and immune-related AEs (irAEs), response criteria (irRC) and endpoints."

Another prevalent research area is rare disease therapies.

This category of high medical need is also associated with high prices, making them attractive for pharma/biopharma companies. The challenge is developing clinical trials for orphan drugs that accommodate the limited patient population. Ms. Stafford of Quintiles noted opportunities lie in how you address those challenges. For example, rare disease registries, where physicians, patients and caregivers record information and track details of the patients' diagnosis, condition and treatment, can address many of the scientific and communication challenges researchers face. Also, patient and caregiver-reported outcomes provide a valuable glimpse into how various treatment strategies impact quality of life. "These insights, which can't be gleaned from labs or physician assessments, often shape the direction of investigations and help validate the choice of clinical outcomes," said Ms. Stafford.

Additionally, as oncology therapies continue down the personalized medicine path, there is a trend towards earlier involvement and better integration of biomarker solutions. "What used to be wholly independent development paths and even teams within sponsors or services contracted to clinical versus lab CROs, is now benefitting from marrying up assay development considerations with early clinical development," said Dr. Zupnick. "Defining biomarkers and associated assays is now essential for targeted patient selection in some first-in-human Phase I/II trials, and presents a novel trend for CROs and sponsors alike, particularly when considering such complexities as joint IND/IDE FDA meetings and companion diagnostic (CDx) development."

Among the many CRO service areas gaining momentum are early phase clinical development protocol designs and risk-based monitoring. A major trend, according to Dr. Zupnick, is the evolution of early phase protocol designs, now more regularly starting to incorporate novel approaches after many years of starts and stops around the 'adaptive' buzzword. He said, "Escalation methodology, such as accelerated titration, is being adopted in lieu of or to supplement the traditional 3+3 structure, ideally to minimize the number of patients exposed to potentially sub-therapeutic dose levels (and of course to reduce timelines)."

He noted, "This design shift in turn presents a level of complexity for CROs that impacts many functions including site selection for what can be highly distinct indications, clinical monitoring and site management for all the changing variables, database design for different assessments and endpoints, statistical analyses, and patient recruitment." According to Dr. Zupnick, a CRO that does not anticipate this complexity in concert with the already rapidly moving and flexible nature of early phase oncology trials will delay study progress while exhausting resources and budget.

Additionally, risk-based monitoring (RBM) is gaining more traction, according to Kristen Snipes, project director, and David Shoemaker, senior vice president, R&D at Rho, "Although many companies don't yet fully understand what trials are candidates for RBM—which can cause angst among both CROs and sponsors—CROs are stepping into an educational role, helping sponsors understand what RBM is, when it is best applied, and what types of monitoring are most appropriate for each trial. Armed with this information, the comfort level of sponsors will improve, and the use of RBM implementation and other monitoring techniques besides 100% source data verification, will increase."

BIOSIMILARS AND OUTSOURCING OPPORTUNITIES

Biosimilar approvals in the U.S. are set to rise in the next few years, while there's a need for greater regulatory clarity, a new U.S. regulatory pathway, called 351(k), is expected to speed the development and marketing of biosimilars, according to Joshua Cohen, associate professor at Tufts CSDD. This process began early this year with the first of nine biosimilars expected to gain approval by 2020, Mr. Cohen added. Within this sector, CROs continue to see activity for analytical services, and as sponsors seek approval in the U.S., anticipate providing much needed regulatory support.

CROs are integral to the development of biosimilars, according to Mr. Lewis at ACRO. "We surveyed our members last year, before the first biosimilar was approved in the U.S.," he said. "At that time there had been 20 biosimilars approved globally and our members had contributed to the development of 19 of them." Members have invested a great deal in building an infrastructure to support biosimilars, from identifying markets, all the way through the development process and regulatory approval and even into market access strategies, he added.

CLINICAL LAB SERVICES MARKET TO REACH $261.4B BY 2020

The global clinical lab services market is expected to reach $261.4 billion by 2020, according to a recent study by Grand View Research, Inc. The demand for early diagnosis in an effort to render effective therapeutic interventions is rising rapidly. A wide range of diagnostic tests in the clinical lab services segment along with increasing rates of infectious and chronic diseases is expected to drive market growth during the forecast period. Additionally, untapped growth opportunities and the rapidly changing healthcare infrastructure in emerging markets such as China, India and Brazil are expected to offer further opportunities in this sector.

Quintiles and Quest Diagnostics recently teamed up to form a global clinical trials laboratory services business by combining their clinical lab operations. The joint venture will offer an expanded range of services and test menu to customers across all segments of the biopharma industry, with Quintiles owning 60% and Quest Diagnostics owning 40%.

The JV combines Quintiles' scale, clinical trial expertise, and therapeutic experience with Quest's operational, scientific and informatics expertise, and supply chain network. The entity will draw upon a team of approximately 3,500 medical doctors, Ph.D.'s and biostatisticians as well as experience, expertise and capabilities in the areas of genomics and precision medicine.

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Mr. Ranade at Pfizer pointed out, "Given the high bar set by regulators for demonstrating biosimilarity, sponsors are likely to want to maintain tight control of development activities and, therefore, will approach outsourcing very cautiously with focused oversight of activities at outsourcing partners. In the analytical arena, routine lot release assays may continue to be outsourced to companies with an established track record of quality performance and on-time data delivery, but the heightened characterization methods (e.g., tandem mass spectrometry, NMR, bioassays), which are at the heart of demonstrating biosimilarity, will generally continue to be performed in-house by pharmaceutical companies."

Now that the promise of biosimilars has finally hit U.S. shores, one would anticipate future investment in the space. According to Dr. Hoffman of Theorem, "Consolidation and acquisition by traditional small and large molecule companies to enter the biosimilar space have signaled the dawn of a new era. Biosimilar development will continue to thrive and one would expect a growth in the preclinical/development space in support of CMC expertise required for these complex molecules. Beyond the registrational trial work, we might also expect to see significant growth in post-approval pharmcovigilance opportunities to meet regulatory commitments."

CROs will likely continue to benefit from the growing global biosimilars market as patents for biologics representing billions of dollars expire or are set to expire soon. Ms. Stafford of Quintiles pointed out, "With the lack of detailed regulatory guidance in the U.S., sponsors of biosimilars products continue to require help with the FDA and registration process as they seek to enter the world's largest market. In addition, the U.S. payer and commercial space is still a work in progress, so there is opportunity there as well."

As U.S. approvals appear to be on a case-by-case basis at present, Ms. Stafford said sponsors will continue to partner with CROs who have access to the latest FDA and EMA thinking as they seek entrance to these large markets.

STREAMLINING DEVELOPMENT THROUGH INDUSTRY STANDARDS

The state of clinical outsourcing today implies CROs play a major part in efforts to streamline drug development. Along with sponsors and other stakeholders, the industry continues to work to drive development times and costs down. An important part of these efforts lies in the establishment of global standards.

"The biopharma industry and its service providers, along with FDA and other stakeholders, have made great strides in improving and streamlining the drug development process," said Ms. Stafford of Quintiles. She highlighted several approaches currently being utilized:

1. Newer design approaches and improving data accessibility to improve the focus on patients, creating better ways to find the right patients for the right trials
2. Modernizing the processes of drug development, including ways to improve the quality and efficiency of clinical trials, reducing timelines by eliminating redundancies and inefficiencies
3. Establishing alternative development pathways to speed the introduction of new therapies to address unmet medical needs
4. Using data to facilitate better clinical trials and to benefit patients

Establishing standards for site accreditation, sustainability, and best practices are needed to help address inefficiencies. Dr. Hoffman of Theorem commented on the progress being made. "Global standards for clinical research sites relating to performance enhancement, common minimal requirements for sites, site sustainability and metrics to achieve accreditation, are all underway across several industry groups," he said. "There is a commonality in approach with phased implementation, consideration for accreditation segmented based on protocol complexity and design, overall risk and specialization required to conduct the trial at a given site. The intent is to leverage all existing guidelines, recommendations and qualification practices already developed." He added the resulting piloting of these aspects noted above will hopefully yield results relating to site engagement, site quality and overall site performance.

Photo courtesy of PPD

ACRO is currently involved in several projects focused on standards and improving drug development. "We are working with TransCelerate on the site training and qualification project to make sure that sites are adequately trained to protect patients and to provide high-quality data. We are also working with the Society for Clinical Research Sites on a variety of projects to improve the interaction, communication and efficiency between CROs and sites," said Mr. Lewis of ACRO. Additionally, ACRO expects to work with both SCRS and TransCelerate on a project to develop a standard site contract.

While some progress has been made, Ms. Snipes and Mr. Shoemaker of Rho point out the pharmaceutical industry is behind most major global industries in terms of standardiza-


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tion, as it's slow to adopt electronic solutions. They added, "Competition, lack of standardization, and the proprietary nature of the data we handle have hindered global collaborations, but by focusing on the product development process as a whole rather than targeting efficiencies within silos, progress can continue to be made."

So, what can CROs do to advance data standards? "The biopharma industry needs us to deliver using standards," said Ms. Stafford of Quintiles. "Groups like CDISC, PCORI and IOM have provided the tools, now we all must speak the language. That means libraries must be developed, processes and SOPs must be reviewed, staff must be trained, and specifications and documents must be created for external providers—the sooner the better. Start with standard data collection tools. Data repositories must be created, mapped and transformed and it will take commitment from non-data people at the top of our organizations."

E-CLINICAL EFFICIENCIES

Needless to say e-clinical solutions continue to have a significant impact on clinical trials, services and partnerships, as well as play a big hand in streamlining drug development and creating efficiencies.

According to Mr. Colvin of PPD, "We are witnessing a remarkable, technology-powered transformation in drug development that holds great promise for revolutionizing how we speed the delivery of safe medicines to patients. PPD isn't a technology company, of course, but in a culture of continual improvement and innovation demands, we work to stay at the forefront of technological change. We are continually evaluating new technology solutions and incorporating the best of them into our operations to help us bend the time and cost curve of drug development for our clients. Our real-time data and analysis technology platform Preclarus enables us to customize and integrate new technologies as they are developed and advanced, such as electronic health records and wearables."

While the advances have been great, and numerous obstacles overcome, certain issues around cost, interoperability, and patient privacy can arise. "Technology solutions continue to evolve and offer efficiencies within the clinical trial development continuum," said Dr. Zupnick of Novella Clinical. "Whether site portals, eTMF, EDC systems with added capabilities (i.e., imaging or risk-based monitoring modules), access to or integration with EMRs, visualization tools, etc., e-clinical solutions offer great promise for improved communication, better safety alerts, proactive trial management, and general study efficiencies. While the impact is mostly positive, cost is a consideration, and we are finding sponsors and sites increasingly spending time on challenges like interoperability, security and patient privacy, which in some institutions can detract from what is an already limited resource for patient recruitment, treatment and clinical trial operations."

E-clinical solutions impact efficiency, timeliness and quality of clinical trials offering integrated, seamless, uninterrupted workflows with greater transparency, according to Dr. Hoffman of Theorem. "The holistic approach of an integrated e-clinical platform is improving and simplifying existing business processes and springboarding paradigm shifts, like remote patient-centric trials," said Dr. Hoffman. "Additionally, transparency of information through advances in visual analytics strengthens partnerships by providing real-time access to aggregated trial data and actionable key performance, quality and risk indicators. As a result, partnerships can become stronger and services can be delivered more efficiently." However, CROs need to be flexible, capable of working with a range of e-clinical solutions to ensure sponsor needs are met.

CROs have built their capabilities from the earliest to the latest stages of drug development with emphasis on partnership, collaboration, and fee for service models. Services continue to evolve as therapies become increasingly complex.

In today's R&D environment there is a greater demand to identify subsets of patients, where treatment related to specific genes is becoming more prevalent. There is also a greater demand for combination product development, where novel delivery systems are being employed to dispense complicated therapy regimens. Additionally, risk-based monitoring (RBM) continues to gain traction and e-clinical solutions are ever more essential to integrate and analyze data, namely predictive analytics aimed at expediting R&D. According to Dr. Hoffman of Theorem, "All companies engaged in drug/biologic and device development will feel these pressures and need these solutions. There will continue to be an increased need for thinkers, not just doers."

Further, in trying to move the landscape forward to develop more drugs in the future, there will be a reliance on collaboration and innovation, as ACRO and CDISC work together on standards for data, quality and security. **CP**