

CRO Trends & Drivers

Specialty Pharma & Biotech Driving Current CRO Growth & Trends

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Biotechnology remains the strongest driver of incremental Contract Research Organization (CRO) revenue growth, followed by Specialty Pharmaceuticals and niche/start-up pharmaceuticals, according to Frost & Sullivan. The Texas-based Growth Partnership company also finds that the US CRO market earned revenues of \$9.77 billion in 2008 and estimates this to reach \$23.78 billion in 2015. The US CRO market has witnessed strong double-digit growth since 2003 and expects strong growth through the forecast period. Before 2003, the market witnessed a sharp drop in growth rates between 1998 and 2002 due to several mergers and acquisitions that led to a decrease in outsourcing relationships of the newly merged entities. There was also a significant slow-down in biotechnology funding from the meltdown of global markets. The markets, however, have since recovered strongly and consistently added over \$1.50 billion in incremental revenues each year. This increase in incremental revenue is primarily driven by growth in R&D spending and the subsequent increase in outsourcing penetration.

There is a strong demand for early stage services from the supply side (R&D spending) that could translate to higher business for CROs if their services are positioned to meet the demand and requirements of sponsors. According to Frost & Sullivan, greater growth potential exists for CROs in early stage work with increased potential for outsourcing, especially in areas such as toxicology studies in which outsourcing penetration is lower. Several CROs are adding early stage capabilities to garner a greater share of outsourcing within this market segment. Companies looking to expand and capitalize on these opportunities,

however, expect to increase capital expenditure and build new facilities or acquire them.

As CROs continue to expand their global presence, they must coordinate closer with IT vendors to ensure the systems are in-line with the rapidly changing requirements of the market. Also, moving forward, we are likely to witness a greater role for CROs in deciding on the IT systems and platforms to invest in as the decision-making moves away from sponsors.

One of the most significant trends within the US, as well as global CRO markets, is the move from transactional to strategic outsourcing by sponsors. The fact that CRO market growth has consistently outpaced R&D spending growth is an indicator that outsourcing penetration is on the rise. It is also interesting to note there have been several preferred partner announcements; the Covance-Eli Lilly partnership being the most recent and interesting one. More deals are expected to be announced, signifying a move toward this trend. These types of partnerships are driven by the fact that despite significant increases in R&D spending, the number of new drug approvals is at a historic low.

Specialty Pharma magazine recently asked some leading CROs to respond to some of the current trends Frost & Sullivan has identified. Participants include John C. Ho, MD, Senior Vice President, Corporate Strategy, Charles River; Andrew MacGarvey, President of US Operations, Quanticate; Richard Walovitch, PhD, Chief Medical Officer, WorldCare Clinical; and Dr. David Kwok, President and CEO, Biopharmaceutical Research Inc.

Q: Specialty Pharma and Biotech have been identified as the strongest drivers of the CRO market. Please describe the type of work you are doing for these types of companies.

Dr. Walovitch: We provide core imaging services to a mix of Fortune 500, Specialty Pharma, and Biotech companies. In 2004, the FDA indicated there had been slow-downs in innovative medical therapy and that imaging could help make the drug development process less costly and more predictable. This resulted in an explosion in the use of imaging as a surrogate marker/direct marker of disease progression in the drug development process. We fit in very well because high-quality reads that we can offer through our strategic relationships become more cost effective over the length of the trial, as the study requires less adjudication and the imaging data better correlate with efficacy endpoints. WCC's 17-year heritage and close relationship with Massachusetts General Hospital (MGH) also means we can read the imaging data that is not yet in full clinical practice. In addition, our in-house radiology team ensures our scalability for processing large volumes of reads.

Dr. Kwok: For the past 11 years, we have been engaged in the development of drug candidates performing a large variety of in vitro/in vivo DM/PK/TK/ADME studies. We also routinely perform bioanalytical LC/MS/MS assay development and validation studies supporting clinical sample assay. Our laboratory is also equipped and routinely performing analytical chemistry CMC studies relating to drug substance and drug product specification assays and stability evaluations.

Mr. MacGarvey: Quanticate is a specialist biometrics company. Our model allows us to offer a range of statistical, programming, clinical data management, and medical communications services. In working with our customer base, we have worked on contracts in which the requirement is a few hours consultancy right through to full-blown support where we might be brought in to get involved with the design of the Clinical Development Program. I find as I meet this type of customer that many of them run with a minimal infrastructure as they seek to slow down the burn rate of their funding. We can help because we are used to plugging into the sponsor's team and becoming an extension of that team while the demand requires it. These customers are very exciting to work alongside as the products tend to be at the leading edge, and so our work needs to be the same.

Dr. Ho: We collaborate with Specialty Pharma and Biotech clients to help bring therapeutic candidates from late discovery through preclinical and into clinical development. Specialty Pharma and Biotech face challenges in both designing and efficiently and cost effectively executing the drug development process. As technology, regulatory requirements, and the biopharma industry continue to evolve, so does the drug development process. We see sponsors exhibiting a stronger desire to migrate/outsourcing services that support development, planning, and project design. This is similar to the demand for CRO support services in the early 90s compared to today's environment, and is substantiated further by our primary industry research conducted by the Tufts Center for the Study of Drug Development. Essentially, the center found that contract research already accounts for more than 17% of total drug development spending, and this number is likely to increase. Specialty Pharma and Biotech expect to work with a CRO to help determine what is essential to accelerate drug development during the critical transition from preclinical to clinical. This is particularly true as smaller biotech and pharma companies carry the responsibility to bring candidate products through clinical proof-of-concept. Continued and increased expertise is required of preclinical and early phase teams to offer tangible value to sponsors. The value offered by our expert teams helps identify appropriate go/no-go decisions earlier in the development process and

provides information to optimize subsequent development. At the preclinical-clinical transition, for example, one specific problem is determining starting doses and escalation multiples, and anticipating key IND review issues. These decisions may not be entirely straightforward, even with the *Guidance for Industry - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* in hand. An experienced CRO with integrated teams can contribute substantially to the discussion. In the current life sciences environment, it is critical to demand and expect more from your CRO.

Q: Early stage work, such as toxicology studies, have traditionally not been outsourced. How are you attracting Specialty Pharma and Biotech companies to reach out to you earlier in the drug development process?

Dr. Kwok: Non-GLP tox studies may not be outsourced traditionally, but GLP tox is commonly outsourced from Biotech and Big Pharma alike. We are able to attract non-GLP tox studies by having developed proven study protocols and best practice procedures for each of the DM/PK/ADME and bioanalytical areas. Another added value is our ability to delivery data more timely and at lower cost than our internal pharma counterparts. One of the strongest drivers for Biotech and Specialty Pharma to work with BRI is their confidence on our scientific ability and their understanding that we deeply care about the success of their projects. This trust is established at an individual level scientist to scientist.

Mr. MacGarvey: This is a very pertinent question for a company that specializes in biometrics, as customers will tend to consider the clinical aspects of the study or program first. We found that there was a demand for consultancy at the early stage and in 2007 established a consultancy arm. This group brings together industry experts, and they are able to provide knowledge around program and trial design early in the process. The main benefit of this is that it leads to efficiencies downstream - critical in a climate in which reducing the cost of the development program is very important.

Dr. Ho: It is important to define early stage work and toxicology. In general, early stage is the series of studies performed to identify the appropriate drug candidate to advance into preclinical development, leading to IND submission and Phase I clinical trials. Usually, these IND-enabling preclinical studies are referred to as toxicology studies and traditionally form a major portion of the work performed by a CRO on behalf of clients. Toxicology studies are regulated and comply with GLP guidelines and, over the past few years, we have seen increasing volumes of these studies outsourced as our clients reduce their internal capacity and staffing. Attracting Specialty Pharma and Biotech companies is key to our growth plans and is driven by continual investment in the technologies required to evaluate the safety of these often novel therapeutic drug classes. Recent technology investments have enabled us to address specific questions regarding biologics, particularly monoclonal antibodies, stem cells, siRNAs, and a wide range of immunomodulators. It is also important for CROs to hire industry-respected experts who are not only technically and scientifically knowledgeable, but also well-versed in the current regulatory expectations and issues for these types of drugs. True early stage development involves supporting drug discovery and lead candidate selection prior to the start of the preclinical toxicology evaluation. This is a sector of the business that has traditionally been conducted in-house or in small, niched, boutique-type CROs. However, we are seeing an increasing interest in having this work done externally with large CROs and to the same degree of rigor, as is expected for clients conducting the work themselves. Feedback indicates that this is seen as a key area that can help reduce later-stage attrition of drug candidates, the primary cause of the escalating cost of bringing a drug to

market. Large integrated broad portfolio providers like us can simplify the transactional complexities and substantially accelerate drug timelines versus using a set of smaller, niche providers. We are working to engage this market through our emphasis on transgenic rodents, surgical preparation of research models, small and large model pharmacokinetic and ADME (absorption, distribution, metabolism and excretion) studies, expanding portfolio of disease and in vivo pharmacology models, and selective acquisitions in areas such as preclinical imaging and oncology specialty providers. We believe that as we continue to build and extend these capabilities, and gain more experience with specific drug classes, it will become an increasingly attractive and cost-effective option for many small-to-medium-size Specialty Pharma and Biotech companies. The impartiality and range of complementary capabilities a CRO can bring to this critical area (that often defines the development and spend portfolio of a company for many years to come) seems to be generating a lot of discussion at senior management levels between the Specialty (and large pharma) companies and CROs.

Dr. Walovitch: In collaboration with current Pharma and Biotech clients, WCC developed a unique new service offering designed to help those that are still in the early stages of the drug development process. The service, called Collect, Ready Hold™ gives study sponsors a way to cost effectively collect, QC, and store images in a central database until it is determined if a central review of the imaging data is required. This approach greatly reduces time and cost associated with a retrospective image collection should the need arise for a central review at the end of a study. We have also received positive feedback on our image library creation and archival service, which allows sponsors to protect important corporate assets by creating a long-term library of image data collected from your pre-trial research, clinical trials, or post-approval activity. All imaging data is archived in the industry-standard DICOM format, enabling immediate access to images and trial data for potential use in future research, marketing, and physician or employee training. Both of these services are unique to our company and are based on our patent-pending WorldPro technology platform. In addition, our strategic relationship with the MGH Radiology team allows us to provide protocol consultation and design services to sponsors in the development stages of their imaging trials.

Q: *What moves have you made to expand your global presence, and how has this affected business with your Specialty Pharma and Biotech customers?*

Dr. Ho: We are seeing the difficult economic climate, increasing market consolidation, and looming patent expirations drive significant industry changes. Pharmaceutical and biotech organizations are realigning their therapeutic focus areas and taking steps to improve R&D productivity. These organizations recognize the benefits of strategic outsourcing, which enables faster, more efficient drug development; reduced need for infrastructure investment; and the provision of expertise, which would be cost prohibitive and inefficient to duplicate or sustain in-house. As a result, we are seeing increasing collaboration as a key strategic partner. By partnering with us on a broader, more strategic basis, our clients are reducing their R&D costs and improving efficiency. To meet our client's needs, we provide drug discovery and development expertise in North America, Europe, Japan, and China. This global network supports our clients' outsourcing model and reduces their need to further invest in infrastructure. In fact, between 2007 and 2009, we opened approximately 1 million square feet of new, customized space globally. In October 2008, to support the growing demand from multinational pharmaceutical clients for outsourced drug development services, we opened a 60,000-square-foot preclinical facility in Shanghai. The new China facility positions us as the strategic partner of choice to fully

support clients' global drug development needs. With this facility, we expect to be the first global preclinical provider offering both discovery and GLP-compliant services in China. In addition, this spring, the company will open the first phase of a new preclinical facility in Sherbrooke, Canada. The new facility will be approximately 300,000 square feet. An estimated 25% will be constructed in the first phase and dedicated to only one or two clients. Through its flexible design, the construction for the remaining phases is timed and designed to accommodate changing market demands. The Sherbrooke facility is ultimately expected to employ 1,000 people, who will work collaboratively with the 1,600 staff currently located at the company's Montreal facility.

Mr. MacGarvey: Our company has its headquarters in the UK, but in response to a demand from our customers, decided to expand into the US. We chose Cambridge, MA, as our base, and as such, have been able to serve the many Biotech and Specialty Pharma companies who are right on our doorstep. To maintain a competitive edge, we have operations in Poland and more recently expanded into South Africa. This global expansion has allowed us to gain the critical mass to support our customers as they progress to bigger studies.

Dr. Walovitch: Through our parent company, ProScan Imaging, we have the ability to use radiologists in Eastern Europe, Asia, India, and the Middle East. And because WorldPro supports readers remotely, we are able to work with the best assessment talent, regardless of the location. To date, we have serviced over 4,000 investigator sites in 50 countries. We can also perform assessment reads for patient enrollment in clinical trials within 24 hours, using our HIPAA-compliant ProScan InteleGRID image upload application. Not only does this expedite the patient enrollment process, but it also ensures that reads can be processed regardless of the location or time zone.

Dr. Kwok: We have provided preclinical development services to biotech and pharma companies overseas in Europe and in Asia. The CRO market outside of North America is largely built on personal contacts with individual outsourcing scientists and business managers who recognize BRI as a CRO with both regulatory experience and scientific expertise in delivering the studies in support of an IND filing. The traditional mass marketing and advertising to overseas markets can be cost intensive and time consuming.

Q: *Frost & Sullivan stated that IT system decision-making is moving away from the client sponsor and into the hands of the CRO. Is this the situation with your clients, and how is that working out?*

Dr. Walovitch: We believe WCC (as the imaging CRO) is responsible for meeting or exceeding all trial-specific needs identified by our client sponsors, and for anticipating future technical trends within the marketplace. Because we strive to do this every day, we take on the role of market monitor, and assume some of the IT decision-making right from the outset. For imaging trials, IT revolves around the image management system, and we addressed many of the typical issues that challenge sponsors with our WorldPro platform, which centralizes image submission, radiology review, and program management in a single system. Unlike many other systems in the imaging trial world, sponsors can control every aspect of transmission and review, including quality control and compliance checks – a huge bonus for reducing IT expenses and streamlining the entire trial. We have received a great response from sites using the system, as well as from sponsors leveraging the flexibility of the tool to support independent panels assessing the blinded radiology

data in comparison to clinical data provided by the sponsor. We also have full-time programmers that develop smartforms: intelligent case report forms that require little to no post-read QC-checking because they don't let the reader fill out the form illogically. These smartforms are designed to maximize the efficiency of the radiologist and minimize the ability to provide incomplete or inaccurate data.

Dr. Kwok: To a large extent, IT system design and LIMS implementation in support of clinical data management is driven by a few large clinical CROs/CRA's that perform the majority of clinical phase development. Some of the dedicated purpose-built LIMS in support of clinical development in Big Pharma and large CROs can be narrowly focused and lacks the broader scope of IT infrastructure to support a small company's project management needs, such as financial and scheduling information. However, for a small CRO that wants the LIMS or IT system becomes a prerequisite to become qualified to do business, rather than a decision based on the merits and suitability of the IT system matching the operating requirements of a CRO.

Dr. Ho: As sponsors increase wholesale outsourcing of clinical development services, they are less concerned with integrating their IT systems and platforms that collect and manage clinical data with those of their CRO partners. Instead, CROs are stepping forward to wholly manage this responsibility. As CROs broaden service offerings, it is less important to our clients which eCRF, data management, and/or analytics systems we use as long as the data and reports measure up with expected quality and standards. Particular consideration is given to systems that exceed CDISC standards, provide a user-friendly interface, and expedite data management activities. Additionally, when clients consider which IT systems to use, they often request and consider input from the CRO. Our clients are, more often than in the past, looking to us as a service provider to supply more data management solutions and base their decisions on the capabilities and robustness of the electronic system(s) we choose. We have also seen with the establishment of the electronic regulatory submission process that there is an expectation to provide data in a format and structure that allows easy and rapid integration into the required format. This has resulted in major CROs to play a key role in these regulatory submission initiatives.

Mr. MacGarvey: I believe CROs have always driven the adoption of technology in our sector, they have been willing to take the risks associated with new technologies as they have moved to improve efficiencies and deliver better service. This makes sense as these providers are always looking to deliver the best product to the customer. What's interesting now is that a lot of the experience with these technologies lies within CROs - people working in CROs have had exposure to multiple systems whilst completing studies for various customers. This gives them a great perspective and allows them to learn the pros and cons of each system. In terms of our customers, we are seeing demand for assistance in vendor selection, system validation, and system implementation. Another big area is integration of technologies and data mapping between systems, we have seen a very large demand for CDISC mapping for example.

Q: *Rising competition and fragmentation in the CRO industry has affected revenue. However, it seems that more preferred-partner relationships vs. transactional relationships have been one of the outcomes of that trend. Are you generating more of these strategic-based relationships with your Specialty Pharma and biotech clients?*

Dr. Kwok: A preferred-CRO relationship is always desirable, and a preferred relationship is always justified by a client sponsor company receiving some form of competitive advantages within that preferred

relationship. For instance, access to exclusive technology or know-how, guaranteed delivery timelines, preferential pricing, etc. In addition to these preferred advantages, the relationship must continue to be built on the CRO's scientific reputation and earned from performing on the job above and beyond the sponsor client's expectations.

Mr. MacGarvey: We have well-established relationships with some long-standing customers, and this has allowed us as a company to learn the very best ways to work at the strategic level. We know what the problems are when a CRO and a sponsor are establishing a strategic relationship and as such can plan accordingly. There is a definite skill to getting the preparation right, not just in terms of contracts but looking at information systems, training, and SOPs. Our experience in these areas, coupled with our critical mass has allowed us to foster more of these relationships. I believe the key word is relationship too. A big driver in a successful partnership is the relationships between the players and that runs from the contracts group right through to operations. Speciality Pharma and Biotech look for a good fit before they will work for you. They don't have the funds or the time to get the decision wrong.

Dr. Ho: As discussed, the economic and patent challenges, as well as market consolidation, are driving significant industry changes. As a result, we are seeing the dynamics of our clients relationships evolve toward broad-based partnerships that help accelerate their drug development programs and drive enhanced productivity and flexibility. At this time, clients are re-examining their core competencies and defining what can be externalized, to focus on what they do best. This focus on shedding non-core activities and assets is shifting the CRO/sponsor dynamics. For example, in our Research Models business, we have a 10-year, \$111.6-million contract with the National Cancer Institute (NCI). In July, we announced the opening of this state-of-the-art 52,000-square-foot facility to support our relationship with NCI while expanding our presence in the Frederick, MD, area. In the new facility, we are working side-by-side with NCI in a seamless partnership to produce the highest quality research models available. The new facility provides genetically defined, pathogen-free mice to support NCI/NIH (National Institutes of Health) funded research targeting metabolic diseases and cancer. In addition, in response to individual customer needs, we have also been flexible in entering into broad based multi-year partnering arrangements, generally involving financial commitments from the customer, which tap into the broad array of physical and/or service resources that we provide, such as reserving dedicated space within existing facilities, building out space to a particular specification, working within our clients' infrastructure, or even establishing a new facility. By partnering with us, our clients realize that working with us can help to lower staff and operating costs while better accommodating changing biomedical research and drug pipeline priorities and demands. We also offer facilities and services providing specialized product and services that are often too prohibitive to clients to maintain in-house. We also are working across the industry on a range of strategic partnerships. By leveraging our extensive portfolio and global footprint, we create substantial impact on our clients' overall R&D and manufacturing productivity. ♦