PERSPECTIVES

Roles of contract research organizations in translational medicine

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Summary

Translational medicine/science is shifting the medical research paradigm from compound-based to evidence-based drug/device discovery. It is increasing interdisciplinary collaborations, enhancing usage of advanced technologies, and facilitating therapeutics reaching patients faster. The fundamental theme of evidence-based discovery is to apply what is revealed in preclinical experimentation and to bring the resulting safety and efficacy to clinics. In the medical fields, a contract research organization (CRO) works like a hired agent who has corresponding knowledge and experience to conduct and complete tasks for a sponsor. The relationship is business, and the contract is for deliverables. The increasingly high volume of sponsored outsourcing work has made this for-profit business boom in the past decade. Location boundaries are being blurred under globalization in the sciences and cross-border regulatory reviews. Getting from bench to bedside is a winding road with many obstacles and high hurdles. Efficient teamwork becomes essential to materialize ideas and bring them to the market. The professionals within team communities include drug/device makers and CROs. It has become increasingly obvious that CROs play pivotal roles in the chain of discovery/design, developing product to market through in vitro, in vivo, and ex vivo testing during preclinical experimentations and clinical trials. Project management teams are responsible for nurturing the materialization in a collaborative manner and enhancing the productivity of the pipelines. CROs have many functional aspects and specialties, and no one organization is fully capable of serving, i.e., integrated services, with expertise in each step of the chain to the needs of a variety of sponsors. Instead of competition among the CROs themselves, the continuously expanding market demands can be shared by Expertise-Based Integrated Services among allied CROs, in contrast to the few large CROs. Empirically, the data generated from the chosen CROs should meet the regulatory requirements for approval. A quality assurance unit from the sponsor should be vigilant in performing audits and inspections of the candidate CROs prior to contracting. Subsequently, close monitoring and well-organized project management guard the path to the successful filing of the applications. A strategic alliance of translational medicine with CROs ensures proven therapeutics for disease treatment and prevention to be connected with patient populations in a timely and cost-effective manner. The unbiased data generated through CROs’ services can be used for a patient-driven approach in drug discovery.

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and device control design. Thereafter, findings from the merged efforts can promote and complete the feedback loop for refining existing medicines and exploring new medicines. A matchmaking business may emerge and evolve from the procurement department of the inventor in translational medicine and the business development sector of the CROs to generate a new landscape in translational medicine.

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**Paradigm shift**

The course of a marketed drug/device after invention is long, winding, and treacherous, and requires significant monetary and intellectual investments. However, with the possibility of detours occurring at every turn, pouring a tremendous amount of time and manpower into this course does not guarantee a successful application's approval by regulatory agencies. Vast research through chemical libraries and a meticulous synthesis of protein to discover medicines have produced a large quantity of bioinformatics. Meanwhile, new and refined synthetic biomaterials for fabricating implantable devices have allowed much improved biocompatibility in the past 2 decades. The fusion between biologics and devices, such as drug-eluted stents and nanotechnology in formulation, has reduced the clear delineation of the two and increased their dependency on each other. Demands from regulatory reviews, clinical practices, and health care operations have pushed for revelation on the mechanism of actions of medicines because of safety concerns, accessibility, and economic considerations. In addition, value generation is a key factor for inventors to convince investors to continue their monetary support, which consequentially models the critical paths of choosing research and development (R&D) processes and setting business milestones. Under these circumstances, translational medicine emerges and therefore manifests the evolved evidence-based medicine [1–9]. Although the regulatory governed clinical trial phases remain the common themes for invention, paradigm shifting has occurred in the early stages of R&D, as illustrated in Fig. 1.

Productivity and valuation are closely related. Mergers and acquisitions (M&As) in the industry of medicine are intended to boost productivity and ultimately attain topline growth [10]. Paradoxically, the evidence has shown that industry consolidation results in less investment in R&D. It is abundantly obvious that R&D outputs, if measured by new medicine approvals, suffer substantially from the reduced investment. Early-stage R&D suffers most from this negative impact owing to the lengthy period required to yield convincing data and the shift in monetary support to clinical trials. It is the attrition of human resources that has led M&As to create tremendous uprooting in organization stability and in scientific continuity. Minute but crucial pieces of information on know-how may be lost during personnel transitions. The remaining staff may face high hurdles in project management to move products in the pipelines. Outsourcing becomes the eminent solution, besides the ineffective cross-functional consortiums.

**Figure 1** Paradigm shift in medicine. The massive searches in traditional approaches have changed to targeted disease mechanistic receptors in the emerging schemes. (Source: Adapted and modified from: John J. Orloff, MD, Novartis Pharma AG, 12 October, 2006.)
formed in each company and among the allied companies, to maintain productivity under these circumstances.

**Contract research organizations**

Prior to and in the early stages of the computer era, contract research organizations (CROs) for pharmaceuticals were utility companies doing large-volume throughputs, conducting toxicology evaluations, and managing clinical trials. They have evolved from the more sophisticated demands of the short-handed medicine and device industries to perform increasingly complex tasks, such as conducting tests to reveal the pharmacokinetics and pharmacodynamics and/or biocompatibility of implants under normal physiology conditions and pharmacological efficacy and/or tissue engineering repairs in targeted disease models.

The continental divide in CROs is preclinical and clinical. The former consists of subdivisions largely grouped into drug screening/design control, compound synthesis/device manufacturing, toxicology/biocompatibility, and efficacy/functional repair. The latter has operations in a flow of phases in human trials to meet regulatory requirements. Although the pharmaceutical industries prefer to hold on to the intellectual properties, M&As and generic products have blurred the delineations that have differentiated companies from brands in the past. Medical industry executives have realized that a faster turnaround to their investment in R&D may come from joint ventures with similar-minded competitors. It is well known that unbiased data should be generated by an independent third party to convince corporate partners and regulatory bodies. The fertile ground for CROs is therefore continuing to expand and has become deeply involved in medical sciences, from concept to commercial stages.

**Collaboration between sponsors and CROs**

There are several common business models for contracts between the sponsor and the CRO. Traditional project-based contracts take up a large portion of all contracts, although increasingly, partnership Full Time Employee (FTE)-based contracts have recently begun establishing a strong footing. Strategic alliances with CROs can build trust and facilitate a more open and frequent communication on project details and priorities, allowing teams to resolve issues from a diversity of business cultures and operational cores.

**Criteria of choosing a CRO**

Sponsors searching for a trustworthy CRO to conduct outsourced work look for corresponding technical competency, quality, turnaround time, and cost. Technical competency represents the capability to perform and experience in conducting similar projects that facilitate the attainment of product development goals. In the era of biosimilars and 510(k) products, familiarity with the targeted commercial product sharply lowers the learning curve, reduces guesswork, and avoids unnecessary failures. In addition, past involvements in similar experiments will help to guide through a swath of obstacles. Quality control and assurance are the two cohesive fundamentals for regulatory filings. They not only delineate good practice in all kinds of operations but also promote the credibility of the obtained data. Satisfying performance in these areas guarantees a smoother and quicker regulatory review process. Well-managed project timelines are crucial to the product development milestones for data collection, which in turn pare overall costs. Aggressively planned Gantt charts commonly cause widespread stress and human error. Consensual logistics management can prepare and control expectations during complex operations. Often, shortcuts and seemingly direct routes increase the monetary investment necessary to patch up holes and/or increase the risk of failure from haste. Commoditizing on contract prices is a quality killer, as additional time and money may be needed to recover from a botched experiment. Needless to say, the impact of this is a major hindrance to the progress of product development in the pipelines.

**Finding the match**

Integrated services from a single CRO would be ideal, which is almost a reproduction of the preexisting environment and operational styles prior to reorganization in the inventor’s facilities. It is obvious that this ideal condition bears the pitfalls of the same in the old systems. Although larger CROs may be able to recruit the best people in specific service areas, the layers of communication involved can become barriers to the smooth progression of discovery/design in product development. The transformation of a scientist in the inventor’s facilities to become a project manager should focus on talent, intuition, motivation, and leadership. This daunting task is like picking a field marshal from ranked generals to lead. Instead, choosing multiple CROs, each of which has its own focused specialties, may become an excellent alternative. That is, programs can be coordinated into a stream by a person with keen scientific instinct and thorough personal communication skills, and make each CRO’s study/technical director the field marshal of a specific segment while materializing the idea to the market.

The concept of Expertise-Based Integrated Service (EBIS), which has been well received by the industry, can be extended to serve virtual companies and academic spin-offs. The allied EBIS CROs, as illustrated in Fig. 2, provide for each of the segments to materialize the idea and bring it to the market. This one-window shopping transaction reduces the anxiety and difficulties attached to scientific knowledge and experience gaps of the project manager/coordinator in the inventor’s facilities and streamlines the process to achieve the goals/milestones in a timely manner. The scientists/managers in these allied EBIS CROs are seasoned professionals who have accumulative knowledge and experience in the identified area/segment. They can perform not only as responsible project managers, but can also serve as program advisors, with skillful hands and intelligent minds. This “ace team” makes missions possible and can overcome obstacles and avoid detours.

PharmaLegacy Laboratories (Shanghai) Co., Ltd. [11] (PL) was cofounded by the authors eyeing this paradigm shift and unique position in the chain of translational medicine. Dedicated disease modeling in preclinical conditions of Bone/
Orthopaedics, Inflammation & Autoimmune, and Oncology becomes one integrally driven part of the EBIS on pharmacology. The installation of an electronic database (IDBS, Guildford, UK) was the first in China; it is used for preclinical experiments at PL and eases concerns over quality and intellectual property. Functional video streaming at PL reduces the distance and spatial issues for its global clientele. The quick renovation of the facility to house a large amount of human disease-related animal models proves the company’s flexibility and its determination to put the clients’ needs first. Tight quality assurance operations ensure that the deliverables meet global regulatory requirements. Open communication and task-oriented teams among the multifunctional cross-trained staff accelerate the conversion from study design to reporting. The operational outcomes have been brilliant, with multiple filings to the Food and Drug Administration and the China Food and Drug Administration (CFDA) and passed audits.

New paradigm

The dust storm produced by M&As continues rolling through the medical industries. The wealth of knowledge and experiences gained in CROs have made them indispensable and able to adapt to engage their own R&D. Although this appears to be a conflict of interest and possibly mutually exclusive, individual successful cases are emerging. This is because of the depth and the infinite inventions of the human mind at the beginning of the chain of translational medicine. Each inventor’s organization has established a group that constantly scouts for new technology to broaden the pipeline, to decode the disease’s pivotal mechanism, and to shorten the development time. In addition, the creativity of the human brain makes the routes to successful marketing on the other end of the chain of translational medicine so versatile that not one recipe is identical to another. Therefore, finding the match for M&As may be a new business model.

New types of CROs are arising. The functions of these CROs are to assist disease diagnosis by various biomarkers, to visualize the progression of the disease with advanced image analysis technology, to formulate the deliverables by maximizing the intended therapy, to target the specific/vulnerable subpopulation by meta-analysis and epidemiology, and to treat patients with a personalized care system. CROs, swiftly evolving in accordance with market needs, have become the essential vehicle to deliver translational medicine [12]. The main recipients of the most beneficial results from this new paradigm are the patients.

Conflicts of interest

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