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FEBRUARY 2016

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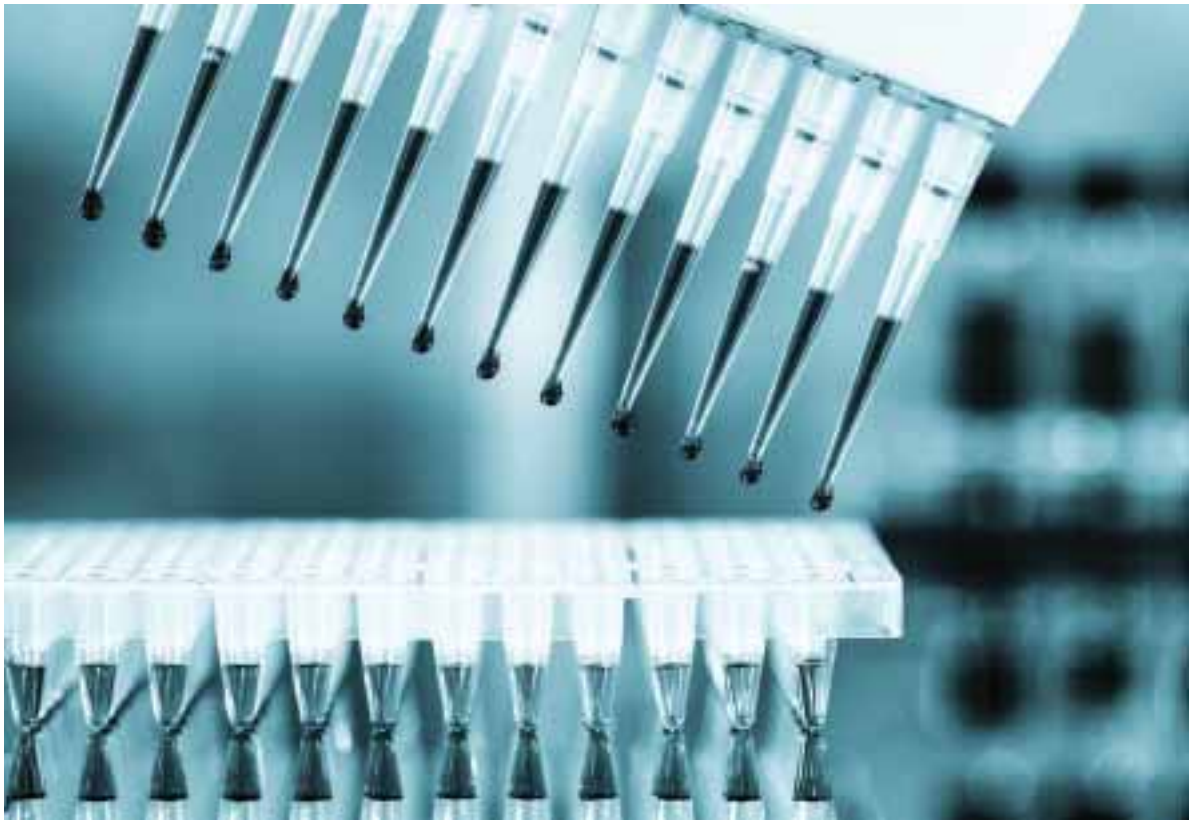

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Aim for the Top

The CRO success stories of the next decade will be the organisations that can keep up with the latest drug development trends and harness new technologies and regulations – and increased reliance on biomarkers seems to be the way forward

Paul Travis at Medpace

The pharmaceutical industry is currently facing major challenges, including patent expiry, generic competition, weak pipelines, spiralling R&D costs, high attrition rates and falling drug approval rates. In response, the drug development landscape is set for significant change in the coming 5-10 years. Most pharma companies and smaller biotech companies have already embraced a biomarker approach to drug development, particularly in areas such as oncology, plus cardiovascular, metabolic, infectious and inflammatory diseases.

Both the FDA, with its critical path initiative, and the National Institutes of Health's Biomarkers Consortium Foundation, recognise the importance of this area of research, and support and encourage the need to continuously develop new and advanced biomarkers, utilising new platforms and tools that can be used not only as surrogate endpoints for registration approvals, but also for internal decision-making during drug development. It is clear that the continuing changes in how drugs are developed will see a marked evolution in the role of biomarkers, and pave the way for an increase in companion diagnostics (CDX).

Personalised Medicine

In 2013, the FDA published 'Paving the way for personalised medicine', in which the importance of biomarkers are outlined, as well as the role these new and evolving technologies will play, while stating the need for quality approach, standardisation and regulatory control.

Achieving success requires a balance between harnessing new innovations, platforms and techniques, and delivering

a quality-driven, consistent and truly global delivery of service. This is set to be one of the most significant challenges the pharma and CRO industry faces, as it sets out to work in partnership to achieve the common goal of developing smarter and more personalised medicines (1).

Integrated Partnerships

Recent feedback from pharma clients indicates that currently "a very fragmented, inflexible biomarker service offering is provided from large CROs and global central labs". Numerous academic, specialist and niche providers are at hand to bolster available resources, but they often do not operate globally, or are unable of scaling up beyond Phase 1. Furthermore, many do not have the resources to operate to Good Clinical Practice (GCP) guidelines, or have College of American Pathologists (CAP) or Clinical Laboratory Improvement Amendments (CLIA) based quality standards in place.

This disintegrated biomarker service also proves expensive, as clinical teams have to individually approach, qualify and contract with multiple niche or academic vendors to fulfil their biomarker and development portfolio needs. A review of the current transactional and niche approaches offered by CROs is presented in Table 1.

Growing Market

According to published research, the current global biomarker discovery outsourcing service market is worth around $2.7 billion, and the current global CDX outsourcing market is about $3.5 billion (2). To meet this demand, pharma companies will increasingly come to rely on external resources, primarily through collaboration and/or partnership.

Many drug companies have also established separate departments to specifically focus on R&D, involving biomarker and CDX as management of biomarker discovery. The development of CDX services requires totally different expertise and technologies than traditional drug R&D, however.

Current Biomarker Services

The diversity and range of biomarkers are such that no one biomarker, technique or platform is likely to have all the characteristics necessary to provide a detailed and robust understanding. In this regard, research providers have responded by offering an extensive range of 'tactical' or single-point solutions to meet a specific need as drugs are developed. Examples are given in Table 1.

This transactional approach gives access to niche and top-class academic services, and allows project teams to 'cherry pick' providers and thought-leaders. However, project teams are then faced with contracting and managing data from multiple providers. Recent examples have seen up to six different biomarker vendors in four countries being utilised.

The identification, development, validation and, ultimately, incorporation of biomarkers into clinical practice is critical to a number of disease areas. Given the complexity of a disease such as cancer, the significance of biomarkers is particularly relevant. A number of biological, chemical and biophysical entities in development can be used in cancer

Table 1: A transactional approach to biomarker services supporting drug development projects

Early development and preclinical support	Biomarker services Phase 1-4	Additional specialist techniques, platforms and services	*In vitro* and CDX development
• Target identification • R&D support • Method validation in different species • Method transfers • Translational and feasibility support • Pharmacokinetics and pharmacodynamics analysis • Novel biomarker development	• Proteomics and high throughput testing • Immunoassay • Flow cytometry • Global project and data management trial support • Development and validation services • Good Laboratory Practice/ GCP/CLIA/CAP laboratories • Biorepository, sample tracking and management • Pharmacokinetics and pharmacodynamics analysis	• Anatomic and molecular pathology • Cytogenetics/ immunohistochemistry/fluorescent *in situ* hybridisation • Genotyping • Next-generation sequencing • Real time-polymerase chain reaction (PCR)/quantitative PCR • Multiplex assays • Circulating tumour cells • Liquid biopsies • Biorepository service, data mining and modelling	• Support and development of CDX, utilising multiple techniques • Regulatory support and guidance • Support for *in vitro* diagnostics (IVD) trials • Validate new instruments for global IVD projects • Good Manufacturing Practice production of IVD kits or CDX

Services offered, managed and contracted through multiple vendors, provided by CROs, central labs, academic or diagnostic labs, no global coverage, inconsistent quality standards, GxPractice, CAP, CLIA, multiple datasets and formats

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diagnosis, prognosis, risk group assessment and treatment stratification, as well as predicting and monitoring response to therapy. While an important focus is on genomics, biomarkers are also being created in areas of proteomics, immunologic metabolomics and epigenetics.

Increasing Necessity

The use of biomarkers has already shown significant success with incorporation into clinical practice for a number of different cancers, including patients with chronic myelogenous leukemia, ovarian cancer, breast cancer, pancreatic cancer, colon cancer and prostate cancer. Given the current emphasis on increasingly precise and personalised medicine, clinical trials in cancer now almost universally include the study of biomarkers as secondary and exploratory objectives (3). Employing CROs, which have an integrated system to the execution of these complex studies, will greatly enhance the probability of successful completion of these studies.

A benefit of utilising biomarkers is the facilitation of having safer and more effective drugs – to guide dose selection, and to enhance their benefit-risk profile. As the FDA states, "Qualification is a conclusion that, within the stated context of use, the results of assessment with a biomarker can be relied upon to adequately reflect a biological process, response or event, and support use of the biomarker during drug or biotechnology product development, ranging from discovery through post-approval" (4). Therefore, the most valuable and useful biomarkers should have the following attributes: suitably qualified; robust; easy to collect; and non-invasive, with adequate stability to ensure they can be processed, transported and analysed while delivering accurate and reliable data.

Project Managers and In-House Services

Crucial to trial success is also the role of biomarker project managers. They balance all facets of the project, including communication with biomarker outsourcing managers plus clinical teams. They further support, coordinate and track assay development and validation timelines, ensuring supplies and logistics are in place to guarantee integration and data delivery on time. However, when the flexibility, consistency and level of customer service offered from the project managers is below standard, it leads to dissatisfaction among clinical teams; it causes delays; budgets overrun; and it is frequently cited as a source of discontentment with vendors.

It is important to note that each of the major global central labs, CROs and niche players has adopted varying methods for providing a full range of services. It is evident that no company can hope to effectively provide all the necessary services in-house to support such a divergent and constantly changing area of R&D. When companies do not offer in-house services, they often look to acquire or seek strategic or joint partnerships with niche specialists in a given field to provide top-class service offerings.

An Alternative Modular Approach

It seems that employing multiple biomarkers – using different techniques and platforms – will be the way forward in order to enable improved prediction of drug efficacy and safety. Selecting a combination of biomarkers and service providers may bring its own challenges, including technical issues on how to integrate results and different datasets; how to control quality; and, most importantly, how to interpret results in different clinical contexts. In spite of these issues, this method is gaining favour with the pharma industry as they seek to gain greater value for money, while utilising top-class services to accelerate their drug development programmes. This collaboration or modular approach is a hybrid of the functional service models that have emerged only recently, and of the full service models traditionally offered by large CRO service providers.

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