Testing Times

Elena Logan of ACM Global Central Lab reviews the history of central labs and gives signs of future direction

No one doubts the vital role that central labs play in the development of new drugs in an industry that was most recently valued at more than $1.5 billion a year (1). The evolution of central lab testing, particularly in the past 10 years, has set the stage for many significant changes and advances for sponsors and labs alike.

The main drivers for progress within central lab services, which are felt throughout the outsourced industry, include the ability to support global clinical trials, increasingly complex protocols, a heavy emphasis on performance metrics, testing and data needs, and a call for overall transparency in the process. All of these drivers stem from pricing pressures and ever-changing regulatory requirements.

The good news is that these types of pressures generate innovative and more cost-effective methods of successfully getting drugs to market. One major benefit for sponsors is simply the choice of central lab partners to conduct global trials; no longer is the market solely dominated by large players. New operational approaches allow sponsors to take advantage of established, regional central labs, while benefiting from advanced data management systems for the centralisation and harmonisation of test data.

Biopharmaceutical sponsors are looking to maximise their investment in clinical trials by testing multiple hypotheses within a single protocol and therefore within a single patient. The advancements of science over the past decade have enabled sponsors to test very specific conditions within a protocol, which greatly increases the complexity of testing schedules and requires more esoteric tests. When all of this is applied on a global scale, logistics are exponentially challenging, especially considering samples must be handled in a temperature-controlled environment and cross borders within 48 to 72 hours.

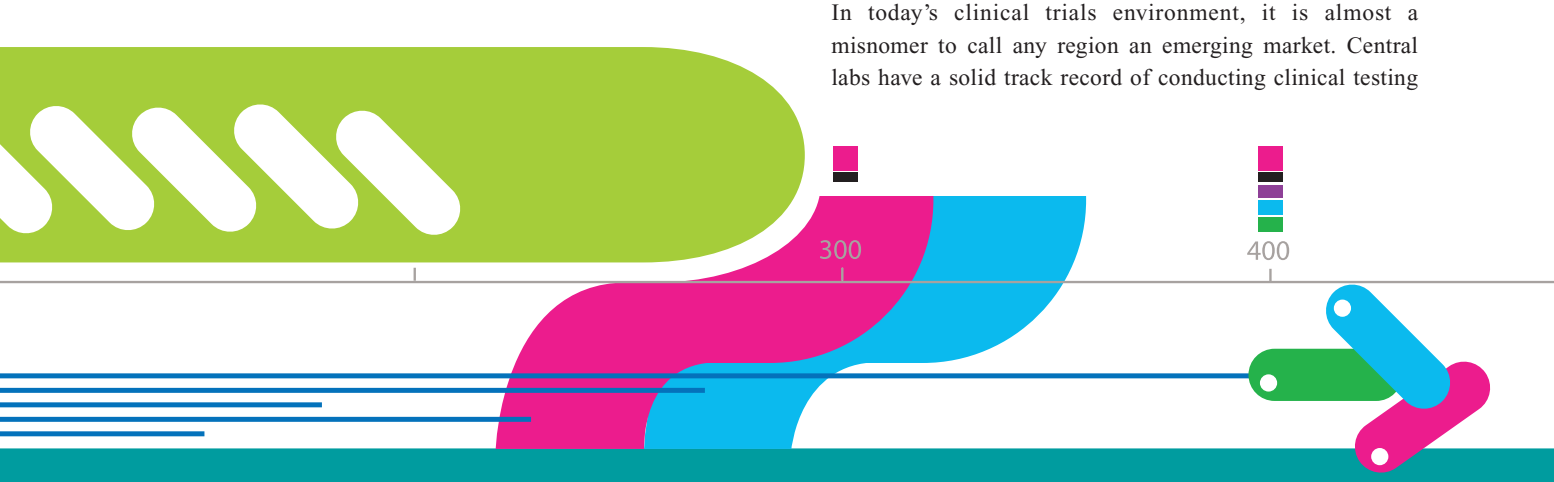
To help sponsors maintain a high quality standard and drive costs out of the system, they are more often relying on metrics-driven performance indicators. Besides the gold standard of the ICH's Good Clinical Practice (GCP) principles, supporting standards and regulatory bodies are providing specific guidance on everything from how to handle specimens to lab test data management.

The results of these drivers are higher accountability and better transparency throughout the clinical trials value chain. Because sponsors have become more savvy purchasers of central lab services, the entire industry has raised its standards to improve overall performance.

It is helpful to take a historical look at how key central lab services – operations, testing, data management and quality assurance – have evolved to gain an insight into where the industry is heading.

NEW BUSINESS MODELS TO SUPPORT GLOBAL TRIALS

In today's clinical trials environment, it is almost a misnomer to call any region an emerging market. Central labs have a solid track record of conducting clinical testing



Central labs have invested in state-of the-art automated delivery and process systems that allow for rapid testing and more standardised results

in regions that were once considered emergent, including Latin America, eastern Europe, India and China. The cost advantages and access to naïve patient populations in these regions are well documented, and central labs are expected to provide coverage on a global basis.

Central labs have historically established their presence in emerging regions by following a linear path. It starts by partnering with a regional lab, and once the volume of business reaches a tipping point, it warrants an investment to build its own lab facilities. However, sponsors are changing their perception of the advantages of wholly owned labs. While data integrity and functional controls are a plus, the depth of testing and regional expertise tends to be limited. Often a new central lab must outsource many tests, which requires harmonisation, and may not have the scientific expertise on staff or the extensive instrumentation often required.

What is emerging as an alternative is a hybrid approach where a central lab forms a partnership with a longstanding regional lab with a broad test menu, a rich database of historical test results and deep regulatory expertise, and establishes a local office with internal staff to manage everything but the test itself. Data is integrated immediately with the centralised database, and shipping and logistics are navigated at the local level, which means tighter specimen controls and lower total costs to the sponsor.

This type of combined expertise has several benefits. Decades of on-the-ground experience enable a regional lab to identify trends or anomalies based on dietary or genetic variations that can affect reference ranges, which may otherwise be missed without the benefit of historical data and cultural expertise. Additionally, regional labs typically have a diverse courier network to handle shipments in the most cost-effective and timely manner, and can play a key role in streamlining the regulatory process with an understanding of local restrictions and requirements.

Another advantage of combining local staff and regional lab expertise is keeping on top of changing tariffs and shipping restrictions. Some regions continually impose higher taxes on clinical trial shipments above regular customs fees, while other countries restrict the movement of specimens across borders.

Fully automated lab equipment with full on-site redundancy delivers powerful productivity and efficiency to provide better medical information. With more information available within 24 hours during the trial, sponsors can make quicker and more informed conclusions for regulatory submissions

With more restrictive regulations and policies in place, sponsors are compelled to maximise their investment with each patient. They are looking at different patient safety pathways and more complex protocols that require elaborate testing methods, schedules and kit assembly and logistics. Central labs are clearly taking on a more active role in helping sponsors develop thorough protocols that extends beyond simply providing the final set of test data.

GOING GREEN

Sponsors are also increasing their 'green' requirements. Nearly all requests for information (RFIs) contain a section to understand a central lab's social and environmental awareness initiatives to lower its carbon footprint. For instance, the packaging of lab collection kits are highly scrutinised, especially when shipping to Europe. Central labs need to demonstrate a commitment to using recycled or sustainable materials and ensure green manufacturing practices, such as alternative wind energy.

GUIDING SPONSORS THROUGH TESTING OPTIONS

As mentioned, testing requirements are increasing in complexity, and therefore biopharmaceutical companies are relying on a more consultative approach to lab testing. Previously, sponsors had internal resources to determine the

assays needed for a protocol, with an emphasis on safety testing. Two major shifts have occurred in this paradigm: more start-up or virtual drug developers have entered the market; and the menu of esoteric testing has grown to include biomarkers and molecular-based assays, such as real-time polymerase chain reaction (PCR), genotyping and SNP testing.

Both large and small sponsors want to understand the latest assays that will help achieve their objectives and, in certain situations, how to cost-effectively conduct a low volume of exploratory tests. Even larger biopharms with in-house testing experience have questions to ask about logistics and operational best practices for global trials.

With the goal of gathering more data from a single patient within the stated protocol, sponsors are more forward-thinking about test data capture. Gathering enough specimens can provide a picture of how a drug will react in their target populations from several angles. For instance, if multiple sclerosis patients express a novel exploratory biomarker during a trial, it may lead to a new focus for the drug discovery group leading to a new approach to treatment or cure and can eventually be introduced in the diagnostic setting.

Central labs are responding by constantly expanding their menu of esoteric and exploratory tests, and staffing more scientific experts who can provide comprehensive test interpretation to help explain certain unexpected results or variation of reference ranges.

Sponsors are now recognising the value of a central lab's on-site pathology and microbiology professionals. Centralised and adjudicated slide interpretation provide standardised diagnosis confirmation and consistent results. Plus, timely confirmation of initial diagnosis allows for the identification of potential clinical trial participants who meet all eligibility criteria, supporting the screening to enrolment timelines. From a logistical aspect, tissue blocks and slides can remain in a single location with the advent of digital technology. Specimens can be located in regions around the world while the reader is located in a central location. This results in tremendous efficiencies both operationally and financially. The need to ship specimens around the world is essentially eliminated, yet the image is transmitted instantaneously.

In the race to get a drug to market, sponsors have increased expectations of turnaround time for lab data. As a result, central labs have invested in state-of-the-art automated delivery and process systems that allow for rapid testing and more standardised results. Safety testing is delivered within 24 hours and even esoteric test results can be provided on more of a real-time basis. With more information available during the trial, sponsors can make quicker and more informed conclusions for their regulatory submissions.

INCREASED DATA MANAGEMENT EFFICIENCY

Over the past 10 years, clinical trials data management has changed significantly. Increased pressure for rapid preparation and review of regulatory submission, and more government and privacy regulations mean sponsors want to review data at any point in time throughout the life of the trial. In addition, the adoption of standards and evolution from paper-based to electronic trials has made a huge difference in the development of data management systems.

The effects of these changes have filtered down to the central labs, which is considerable, as it has been estimated that as much as 60 to 80 per cent of the data generated during a clinical trial is data (2).

The Clinical Data Interchange Standards Consortium (CDISC) Lab Model is one standard that has gained traction in the market for the capture and interchange of lab data. Although standards adoption has been slow, more companies are now upgrading or replacing legacy systems that incorporate these standards.

For example, organisations can enhance their data management systems to support the CDISC standard, and for sponsors requesting the data in a standard format, teams can decrease development time by up to 60 per cent. Standards provide a common language to quickly establish the desired format for better data analysis. Definitions to even common data fields, such as order number, sample number and Kit ID, are reconciled from the onset to enable the data to successfully map to the sponsor's central data management system.

Even when sponsors develop their own variation of a standard, central labs are more efficient with the development process and experience improved data quality. This is particularly important for central labs to avoid contractual financial penalties relating to data quality, which have become more prevalent. Standards like those from CDISC help ensure that the structure of the data is compliant, and aids in the quality control process.

REAL-TIME ACCESS TO DATA

The next step is data integration. Combining the power of the internet and adoption of standards is making real-time clinical trial data integration feasible. The benefit that sponsors can reap today is the real-time access to test data, which is now an expected capability from a central lab. Sponsors require 24/7 access to data to monitor results as they come in with the option to view them in different units. This enables sponsors to be more proactive in managing their study and frees up the central lab to focus on data quality for the final transfer.

EXTERNAL & INTERNAL QUALITY ASSURANCE METRICS

Similar to the effect that CDSIC has had on data management, the Metrics Champion Consortium (MCC) is affecting how performance is measured, including specific metrics around central lab services. Setting performance expectations and opening up honest dialogue between the central lab and the sponsor ensures a high level of accountability.

To keep the balance of clinical research and ethical principles in light of complex test requirements, central labs have an obligation to ensure that patients are informed of what tests are being conducted for the current trial and what future testing might be performed on their specimens, particularly if it involves genetic samples.

The mission of MCC is to develop performance metrics with the intent "to jointly encourage performance improvement, effectiveness, efficiency and appropriate levels of controls for both sponsors and service providers in support of the drug development process" (3). The 14 published Central Lab Metrics are now more frequently requested by sponsors and cover everything from lab operations to data cleaning to quality assurance (QA).

In order to achieve a high ranking on these metrics, central labs are also developing internal benchmarks that are focused on preventing issues before they become problems. For example, while the QA metric of "percentage of on time accepted file transfers" is important, central labs need to have internal SOPs to ensure that the quality of those on time file transfers meets the sponsors' requirements the first time. A follow up QA metric would be the "percentage of clean data sets delivered in the format expected," which requires feedback from the sponsor.

GUIDING PRINCIPLES

Central lab QA has always been performed in accordance with GCP principles, yet those guidelines do not specify central lab services' requirements. It is up to the individual lab to interpret and apply those principles accordingly. For instance, tests must be reported within the expected turnaround time. Not only is that what the sponsors require, but it also protects the rights, safety and welfare of subjects. A patient is on the other side of a specimen and a lab test and, depending on the trial, may be getting treatment for a serious condition.

About the author

Elena Logan, VP of Clinical Trials at ACM Global Central Lab, has 20 years of experience in clinical research, including clinical operations and business development for Big Pharma and the CRO industry. She started her career as a Clinical Scientist at Bristol-Myers Squibb and moved into business development with roles within the CRO industry. Elena currently sits on the Bioscience Workforce Development Advisory Board at Rochester Institute of Technology's (RIT) Center for Bioscience Education and Technology. She earned a BS in Chemistry from LeMoyne College. Responsible for global sales and operations at ACM Global, Elena has been instrumental in the overall growth of the clinical trials testing business and is an advocate of innovative and efficient central labs services. **Email:** elogan@acmgloballab.com.

The MHRA released a landmark guidance document in July 2009 on the maintenance of regulatory compliance in laboratories that perform the analysis or evaluation of clinical trial samples. It provides very specific terms on how to apply GCP to central lab services, including study conduct, patient safety and informed consent. With informed consent, for example, it explains the role of a central lab in ensuring that no testing is performed that is not explicitly described in the protocol or consent form.

To keep the balance of clinical research and ethical principles in light of complex test requirements, central labs have an obligation to ensure that patients are informed of what tests are being conducted for the current trial and what future testing might be performed on their specimens, particularly if it involves genetic samples.

FUTURE DIRECTION FOR CENTRAL LABS

The industry has seen the central lab market evolve into a full-service provider of clinical trial testing. More options than ever before exist for sponsors to select the best central lab partner to fit their needs. The constant changes in testing options and more complex protocols place central labs in a more pivotal role to affect the conduct of a trial. Data management standards will continue to play a major role for true e-clinical data integration, which has the potential to significantly decrease time-to-market for drug development. The push for performance metrics will raise the overall quality of clinical trials as long as the sponsors and labs agree on the right benchmarks to be measured.

With the efficiency gains from the outsourcing model for sponsors, central labs will continue to develop core competencies in the growing complexity of lab testing.

References

1. Barrett R, Cocker DJ, Daniel E, Hughes G, Miller C and Stiles T, *Central and Core Laboratories: The Definitive Guide to the Current Status and Future Prospects of Central Clinical Pathology, ECG and Imaging Laboratories*, BioPharm Knowledge Publishing, October 2007
2. Bassion S, The CDISC Lab Model: Saving Users Time and Money: Central laboratories are realising significant cost and time efficiencies by using standardised data, *Applied Clinical Trials* November 2005
3. Metrics Champion Consortium, http://www.metricschampion.org