When Is It Appropriate to Outsource Bioanalysis Work to a CRO?

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When considering whether to outsource work to a CRO, there are a number of factors to assess, including the type of work that may be outsourced, regulatory considerations, and needs for the study.

As a drug moves through the development and regulatory pipeline to approval, a sponsor may choose to outsource some or all of its bioanalytical work for a variety of reasons. Some biopharma companies may be virtual and need to outsource everything. Others may have the capabilities to do the work in house but choose to outsource for financial or other strategic reasons. When a sponsor chooses a contract research organization (CRO), it may be looking for a partnership, while others may simply be in need of a service and the relationship is strictly transactional. Whatever the situation, a sponsor should consider its own needs, capabilities, expectations, and limitations when choosing a bioanalytical CRO.

Not all CROs are the same. There are the niche or specialty CROs and the "one-stop-shop" CROs. CROs may cover a wide range of offerings outside of bioanalytical such as clinical trial management, central lab activities, manufacturing, etc. There are also CROs that solely provide bioanalytical services. Some may specialize in certain therapeutic areas or have special equipment to perform specific types of assays. Others will be best suited for pre-clinical development studies and some for long-term, high-volume clinical trials. Small CROs may not have the capacity to accommodate several large-scale studies and also support other clients, while some larger CROs may hesitate to commit to smaller studies that could interfere with their commitments to large studies. In this case, the choice of CRO is then narrowed. The bioanalytical laboratory location and cost of services also may be limiting factors in the decision to choose a CRO.

Throughout drug development, a number of labs may be required for various stages (see **Figure 1** for examples.) Pre-clinical studies are necessary to support investigational new drug (IND) filings and clinical trial design. Bioanalytical good laboratory practice (GLP) studies are expected to be conducted with the proper quality systems in place to ensure the integrity and reliability of the data. Early development work also may include exploratory biomarker assay determination, to be narrowed down for eventual clinical endpoints and companion diagnostics to be co-developed with a therapeutic. Given the need for rapid data turnaround for decision-making purposes, factors to consider when choosing a CRO for early development studies may include the capacity to meet critical timelines, as well as the future prospects of entering into a partnership for clinical studies.

Clinical development includes first-in-human (FIH) through Phase III studies. Bioanalytical programs become more complex with good clinical practice (GCP) regulations and often utilize a central laboratory for sample processing. Bioanalytical strategies include pharmacokinetic/pharmacodynamic (PK/PD), anti-drug antibody (ADA) and biomarker assessments, as well as the use of a cell culture lab for neutralizing antibody (NAb) assays.

Regulatory considerations for clinical development include safety and efficacy data for regulatory agency filings and medical device application data for companion diagnostics (if applicable).

Clinical programs can last many years, be very large, and include studies in different populations as well as genotoxicity, reproductive toxicity, and carcinogenicity studies. Not only are there considerations for bioanalytical assay development, validation, and sample analysis, but other items for consideration include long-term sample storage and assay lifecycle maintenance for critical reagents. Choosing a CRO with the capacity for developing, validating, and analyzing high-through-

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ISSUE OF PHARMACEUTICAL TECHNOLOGY®. WWW.PHARMTECH.COM.

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put studies per regulatory guidance and the stability to accommodate the needs of a longitudinal study are factors to consider for clinical studies.

Post-marketing requirements (PMRs) and post-marketing commitments (PMCs) are part of a post-marketing study that may be requested by regulatory authorities at the time of approval or after approval if new safety information becomes available. These studies may be observational and meta-data driven or may require additional clinical trials needing bioanalytical support for safety and efficacy data in different populations, as well as long-term studies for vaccines and cell and gene therapies. Agency-required studies are often timebound. Failure to comply with post-marketing requirements could lead to regulatory agency actions. The choice of CRO for these studies may be based on current relationships, because utilizing the same CRO that performed the previous clinical studies would be most appropriate, given their experience with the study(ies) and lifecycle maintenance of the assay methods and reagents. For special indications, a CRO that has specific expertise in a certain therapeutic area or in a specific patient population might be required. The choice may come down to which CRO has the capability and capacity and can commit to meet critical timelines.

Outsourcing by data need

Throughout drug development there are many different opportunities for bioanalytical data acquisition. Drug concentration, drug target, anti-drug antibodies, biomarkers, drug activity assays, drug metabolites, biomarker metabolites, genetic markers, and genetic mutations all represent the variety of data needs for a therapeutic to reach the market. All or some may be of interest and/or required for a sponsor to fully understand the effects of their drug. Large molecule, ligand binding PK and ADA assays are common in practice across industry and don't necessarily require special equipment. However, some may require instrumentation that not all CROs have access to. For example, some biomarkers require high sensitivity that must have specific specialized instrumentation to assess at pico- or even femtogram levels. Mass spectroscopy, cell labs, and molecular biology labs are not a given at all bioanalytical CROs. The needs for these assessments may be a consideration when choosing a CRO, if the preference is to outsource to multiple CROs versus one that offers a variety of analysis platforms.

Figure 1. Sponsor needs by phase.

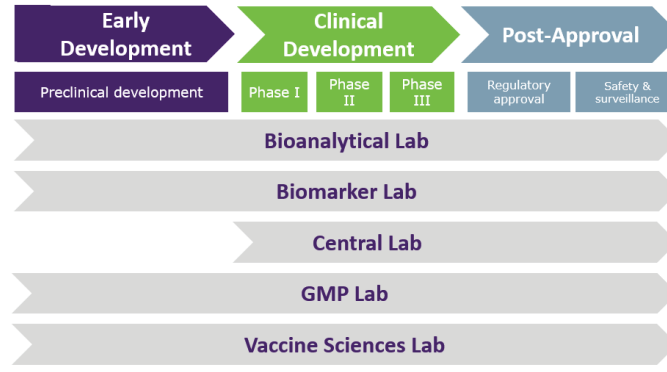

FIGURE COURTESY OF THE AUTHORS

With the number of therapeutics coming to market, industry is seeing increasingly complicated modalities and compounds. This requires not only regulatory and analytical expertise but scientific expertise to ensure accurate method development and analytical oversight for a program. As the complexity of biotherapeutics increases so does the need for innovative technologies and platforms to address the bioanalytical needs of getting a drug to market. Particularly for long-term programs that are not technically standard, scientific oversight of method performance will be necessary. While the sponsor will have ultimate responsibility of the final data reported, scientists at a CRO will be responsible for the initial assay development and optimization and act as the first line in identifying trending changes, technical assay challenges, and can assist in risk mitigation if needed. Scientific experience and knowledge in a CRO are imperative to a successful clinical trial.

The CRO will likely follow specific regulatory requirements and guidances for assay validation, data management and reporting, sample handling, and equipment and IT systems validations and maintenance support, depending on their laboratory specifications. Some examples of common documents include:

- FDA, *Bioanalytical Method Validation Guidelines*
- FDA, *Guidance for Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products*
- European Medicines Agency (EMA), *Guideline on Bioanalytical Method Validation*
- Guideline on Immunogenicity assessment of therapeutic proteins
- US, *Code of Federal Regulations* Title 21
- International Council for Harmonisation, E6 *Good Clinical Practice: Consolidated Guidance.*

In addition, CROs may be certified by the College of American Pathologists (CAP)/Clinical Laboratorty Improvement Amendments of 1988 (CLIA) or follow GxP regulations and be regularly inspected by the FDA, the Brazilian Heath Regulatory Agency (ANVISA) or other similar regulatory bodies. When considering the bioanalytical needs of a program, it is not only important to have expertise, instrumentation, and capabilities, but the infrastructure of the organization and the security of processes to ensure the integrity and safety of data.

Choosing the right CRO is an important decision and can be instrumental in a successful drug development program. Capacity needs, expertise, regulatory knowledge, or timelines may drive decisions. Whether it's a one-stop shop or a specialty CRO, all CROs should adhere to best practices, standard operating procedures, and regulatory guidance to assure quality and integrity of the data. **PT**