Gaining Analytical Insight in the Development of Biologics

Contract testing organizations can provide bio/pharma companies with a cost-effective way to adapt to new technologies and regulations.

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Improvements in analytical technologies provide increased capabilities to examine proteins, cell lines, raw materials, and drug product throughout the drug development and manufacturing process. Regulatory expectations have also evolved. These new analytical requirements can tax the resources and technical capabilities of drug companies.

Contract testing laboratories, which traditionally provided specialized testing services and expertise, are playing new roles in the current biopharmaceutical development market. To gain insight on what sponsor companies can gain from outsourcing their analytical processes, *Pharmaceutical Technology Europe* spoke with Jure Kapetan, managing director Eurofins BioPharma Product Testing D/A/CH; Wei Pan, director strategy and analytical CMC, development and analytical services, and Michael Merges, director of strategic growth, biologics analytical services, both at Catalent Pharma Solutions; and Alex Perieteanu, director, biopharmaceutical services, Natalia Belikova, analytical services director, and Bérangère Tissot, general manager and manager Biological Sales; all at SGS Life Sciences.

Outsourcing brings expertise and capacity

PTE: What are the benefits of outsourcing analytical processes?

Pan and Merges (Catalent): While the outsourcing of small-molecule analytics is commonplace and the infrastructure of development partner/sponsor collaborations is extremely well developed, the same is not true for biologics. Recognizing this, outsourcing partners have invested heavily in both expertise and technology to analyze biologics within full compliance of all regulatory requirements. This concentration of scientific expertise and capital-intensive specialized technologies are making earlier and broader biologics-based testing more efficient at contract development and manufacturing organizations (CDMOs) than it has been previously. Many of these companies now have the technical capability and capacity to bring some analytical testing forward in the development timeframe and to progress biologic candidates into clinical testing very rapidly.

Perieteanu, Belikova, and Tissot (SGS Life Sciences): The biopharmaceutical landscape continues to rapidly change as new technologies become available, new regulations take effect, and as markets expand. To remain competitive, companies must adapt rapidly, which brings high infrastructure cost, knowledge costs, and risks dilution of focus and internal resources.

The key benefits to outsourcing are the ability to leverage the externally existing infrastructure, expertise, knowledge base, and flexible resources of the provider. These resources include a breadth of instruments and capabilities that are not always possible or feasible to invest in internally. A contract research organization (CRO) is usually proficient in a wide number of techniques, and if they have successfully passed their regulatory inspections, can offer a high level of confidence to sponsors that its processes and procedures are proficient and applicable to a variety of products. A CRO's cost and timelines can also be managed by contracts and controlled more rigorously than a sponsor's internal spend can be.

Kapetan (Eurofins): There are many benefits of outsourcing that our customers recognize. On a more basic level, outsourcing analytical services can provide temporary relief if the customer's in-house [quality control] QC lab is experiencing high backlogs due to fluctuating workloads. In these cases, it can be very convenient to have a trusted laboratory to outsource overflow work to in order to decrease the volume for the in-house lab, thus facilitating the ability to meet tight turnaround times. On a more strategic level, having a long-term outsourcing partnership can not only minimize overhead costs (i.e., staff, capital expenditures for specialized equipment, etc.) but the right testing partner can also provide access to

scientists with expertise in various areas for targeted methodology and management of high priority projects that cannot otherwise be handled in-house. Outsourcing analytical services can also help to eliminate conflict of interest by separating the QC testing from the in-house manufacturing operation.

PTE: What changes are you seeing in the industry regarding the outsourcing of analytical services?

Perieteanu, Belikova, and Tissot (SGS Life Sciences): We are witnessing greater demand from clients for integrated services, meeting ever shorter timelines to reduce the development cycle of new drugs, and requests for more complex services such as characterization and analytical similarity.

The biosimilar space continues to grow, and because of a desire to remain lean, rapid, and versatile, there is an ever-increasing number of near virtual companies that have adopted a pure outsourcing model. Being the first to market with a biosimilar stands to reap the greatest reward, and many depend upon this financial model. Analytics are arguably the main cost component in biosimilar development, and because CROs can offer off-the-shelf expertise, platform analytics for characterization, and routine testing, there is considerable time and cost advantage to the outsourcing model. However, for clients requiring analytical guidance, regulatory feedback with regards to analytical methods, risk assessment, or analytical method lifecycle management, bespoke models can be offered that are more than just fee-for-service.

PTE: Which analytical services are requested most often by bio/pharmaceutical companies?

Pan and Merges (Catalent): Our biologics partners are often looking for full turnkey analytical solutions to assist with the development of their new molecules. The most requested niche capability is bioassay development. In the small-molecule area, the pharma outsourcing model has changed in recent years. Traditionally, big pharma only outsourced late-phase and routine programmes to analytical testing labs and retained early-phase method development projects and problem-solving activities in-house. Recently, however, we have noticed that our partners are transitioning many of their bench scientists from lab work to direct management of outsourcing activities and are outsourcing their analytical work at much earlier phases of product development.

Perieteanu, Belikova, and Tissot (SGS Life Sciences): Interestingly, it tends to be less about the analytical technique itself, but more about the application of the work being conducted. Applications that lead to patents that can have an impact on patient safety, that provide data on the efficacy, the biosimilarity of the product, and/or ultimately are included in regulatory submissions have certain requirements in terms of their study design and level of quality. Because of the criticality of such applications, you often see those studies being outsourced to CROs.

Challenges in biologics

PTE: What challenges in analytical testing have developed in recent years? How can companies address these challenges?

Kapetan (Eurofins): The biggest challenge in recent years has been ensuring compliance with the most up-to-date regulations specific to data integrity. This has required that companies perform gap analysis for each individual software system, including but not limited to: audit trail management, data backup, system security (i.e., passwords, access rights, etc.), and incident reporting and change management. The gap analysis is intended to identify remediation activities required for each individual software system, and then those remediation activities will need to utilize the industry standard ALCOA [attributable, legible, contemporaneous, original or true copy, accurate] principles identified in recent MHRA [UK Medicines and Healthcare products Regulatory Agency] and FDA [US Food and Drug Administration] guidances around data integrity. This process has been and continues to be time consuming and will require significant resource investment throughout the industry.

Perieteanu, Belikova, and Tissot (SGS Life Sciences): As the biopharmaceutical industry matures and diversifies, we are beginning to see more and more cell, gene, and other advanced medical therapies alongside the more traditional vaccine, enzyme replacement, and immunotherapy products. The analytics and the analytical strategy required for each continue to develop and mature as the industry and the regulators better understand and define the controls and monitoring required to ensure all critical product quality attributes are met. Having the right knowledge base and analytical tools available is essential for companies entering these markets.

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— Jure Kapetan, Eurofins

Pan and Merges (Catalent): There are a few challenges that come to mind. The first two are the velocity at which technology is evolving and the increased volume of data being generated. Technical advances by instrumentation vendors and follow-on capital investments have allowed Catalent to reduce analytical testing turnaround time in many cases whilst providing more extensive data packages. The additional challenge is in training and retaining qualified scientists. Catalent places a lot of emphasis on scientific training, collaborative problem solving with partners, and continuous education, including through participation in conferences and trade shows.

PTE: How has the surge in biologics development affected the analytical services you provide?

Kapetan (Eurofins): The surge in biologics development has led

to an increased demand for rapid testing methods, as well as the setup of automation systems, in order to meet tight turnaround times and cost-effectiveness in biopharmaceutical analytical testing. The rapid testing comprises impurity testing methods, such as sterility and mycoplasma testing, as well as ELISA [enzyme-linked immunosorbent assay] and cell-based bioassays by qualified automated systems. Off-the-shelf methods and platforms are available and can be adapted to the requirement of each biopharmaceutical molecule.

Pan and Merges (Catalent): Pharma companies have tried shifting their own key internal resources from small molecule to biologics programmes, but the skill sets required for performing niche biologics analytical services such as bioassays are scarce. Using bioassay as a further example, Catalent has turned to automation of both cell-based assays as well as molecular binding assays to provide additional capacity. We are now planning to apply additional automation to the manufacture of analytical cell banks for bioassays.

Perieteanu, Belikova, and Tissot (SGS Life Sciences): In recent years, one focus of note was the diversification and enhancement of our structure and function analytical capabilities, which include development of services such as hydrogen deuterium exchange with mass spectrometry (HDX–MS), biolayer interferometry (BLI), surface plasmon resonance (SPR), and upgrading of our flow cytometry capabilities. In the coming years, we anticipate multi-faceted growth both in the traditional products, biosimilars, and in advanced medical therapies. Our goal is to maintain an industry lead, and to ensure that the one-stop shop of today expands to be the one-stop shop of tomorrow.

New technologies and regulatory requirements

PTE: Are there new analytical technologies being developed? If yes, how will these impact the industry?

Perieteanu, Belikova, and Tissot (SGS Life Sciences): We have been developing orthogonal analytical tools to work alongside the classic structure and function biophysical, biochemical, and biological techniques. HDX–MS services, in combination with BLI, and SPR, better equip us to investigate key structural characteristics, or changes that impact biochemical potency.

The pharma and biopharma companies are now at a stage when some of the methods that were deemed fit for characterization only are now entering the QC arena:

- Intact molecular weight by mass spectrometry has replaced the sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS–PAGE)
- Peptide mapping by liquid chromatography–mass spectrometry (LC–MS) is replacing the Western Blot and ultraviolet (UV)-based methods
- The multi-attribute methods based on peptide mapping by LC–UV–MS are on the verge of replacing a multitude of the most QC-established methods such as chromatography and capillary electrophoresis.

It is still challenging from a compliance standpoint to bring such complex equipment and software into a QC environment. Additionally, from more of a characterization standpoint, methods that were deemed as being 'academic' are now making their way into the biopharma industry, with two-dimensional nuclear magnetic resonance spectroscopy (2D–NMR), HDX–MS, or ion mobility mass spectrometry being among these.

Kapetan (Eurofins): New analytical technologies are being developed in order to perform testing on finished products that incorporate drugs with microchips. QC testing will not only be required to assess the drug performance and specifications but will also need to determine if the microchip is functioning as intended. This will require modifications to existing standard equipment for certain tests and will require new regulations and standards to keep pace with this new technology.

Pan and Merges (Catalent): Yes, there are many new technologies being developed. Some have been rolled out and acquired by Catalent such as the automation mentioned previously, mass spectrometers for extensive deep characterization of biologics, extractables and leachables and trace metals, and automated data acquisition software technologies. In [the] small-molecule area, the application of existing non-traditional techniques such as evaporative light-scattering detection (ELSD), charged aerosol detection (CAD), electrochemical, conductivity, [and] refractive index coupled with multi-angle light-scattering (MALS) detection are on the rise with the increasing number of either poorly soluble or difficult-to-detect compounds entering the development phase.

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—Perieteanu, Belikova, and Tissot, SGS Life Sciences

PTE: What are the top things companies should be doing when it comes to analytical method development?

Pan and Merges (Catalent): It is critical for companies to establish a strategy and partnership with the CDMO to provide continuous assurance that the methods developed remains fit for its intended purpose during the lifecycle of the product. As the development programmes advance from Phase I, Phase II, Phase III, and commercialization, a comprehensive review must be done for each stage to evaluate the need to optimize the analytical procedure or to revalidate all or a part of the analytical procedure. Even after a product recieves FDA approval and becomes a commercial product, FDA still requires a trend analysis on method performance be performed at regular intervals.

Perieteanu, Belikova, and Tissot (SGS Life Sciences): We have all heard the statement, 'fit for intended purpose,' and many laboratories have well established procedures paralleling International Council for Harmonization (ICH) Q2(R1), which defines 'fit,' but few have procedures discussing the requirements of 'intended purpose.' Arguably, one is of no use without the other. Companies should be taking a holistic look at method development and incorporate key elements of quality by design (QbD).

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Defining up front the direction of any programme's development is crucial:

- Know your product: there is a great deal of method development that can start on paper in the preparation of the development
- Understand what is the purpose of the method: define what attributes need to be characterized or monitored relevant to the stage of development the product is at.

A method that is well developed is a method that is efficiently validated and applied to routine testing, so investing the time and money will lead to greater success.

Kapetan (Eurofins): The current trend in method development is to utilize a QbD principle. This is define in ICH Q8 (R2) but is geared toward manufacturing processes. However, the same principles can be applied toward analytical method development. Following a QbD approach stresses a thorough understanding of the method requirements, enforces that the method is fit for purpose and robust, and supports evaluation of the method throughout its lifecycle. Defining expectations for a method prior to initiating development guides the science of method establishment. Once initial method conditions are established, they must be thoroughly evaluated to ensure that the method is both rugged and robust. Ensuring so during method development increases confidence in the method prior to performing method validation. Evaluation of the method does not stop after successful validation. Monitoring of method performance should continue throughout the lifecycle of the method and should result in optimization of method conditions should performance change. Another best practice for method development is to establish the robustness of the method by using a design of experiments. In the past, robustness would be evaluated by altering individual parameters to observe impact on method performance. Using a design of experiments approach allows for multiple parameters to be statistically assessed simultaneously.

PTE: Have there been recent changes in regulatory requirements, either in the US, or internationally, that have impacted how you perform analytical testing and/or method development?

Kapetan (Eurofins): While the QbD approach discussed is not specifically written for analytical methods, the major regulatory agencies expect this approach to be applied to the method development arena.

Pan and Merges (Catalent): The *Unites States Pharmacopeia* (*USP*) introduced new General Chapters <1032>, <1033>, and <1034> [that] address the design, validation, and analysis of bioassays respectively. ICH Q3D *Elemental Impurities* disclaimer icon guidance, and *USP* General Chapters <232> Elemental Impurities—Limits and <233> Elemental Impurities—Procedures reached their official implementation date for new and existing human drug products. Starting 1 Jan. 2018, all [new drug applications] NDAs and [abbreviated new drug applications] ANDAs for drug products with an official *USP* monograph are required to meet the requirements described in <232> and <233>, and applicants submitting new NDAs and ANDAs for non-compendial drug products are expected to follow the recommendations in ICH Q3D. PTE

AMRI to Expand Container Closure Integrity Testing Services into EU

On 22 Feb. 2018, AMRI, a contract research, development, and manufacturing organization, announced the company is expanding its container closure integrity testing (CCIT) services into the European Union (EU). The company intends to build out custom laboratory space for CCIT in its Valladolid, Spain analytical facility. Additional analytical services, including reference standards and International Council for Harmonization (ICH) stability testing, will follow later in 2018.

"Within the last several years, the life-sciences industry has pivoted toward quantitative methods for integrity testing of sterile package systems, with regulatory agencies increasingly demanding these more modern technologies," said Mark Stier, head of analytical services at AMRI, in a company press release. "As our client base for this critical service continues to grow in Europe, this expansion is a logical step in our mission to provide comprehensive testing solutions to customers across the globe."

The company expects that the expansion of these services to the EU will complement its existing local capabilities in chromatographic analytical method development and the future build-out of reference standard ICH stability facilities at the site. The expansion strengthens the company's ability to provide services to European customers and to deliver a more comprehensive solution for drug discovery, development, and manufacturing.