Analytical Support for Biologics

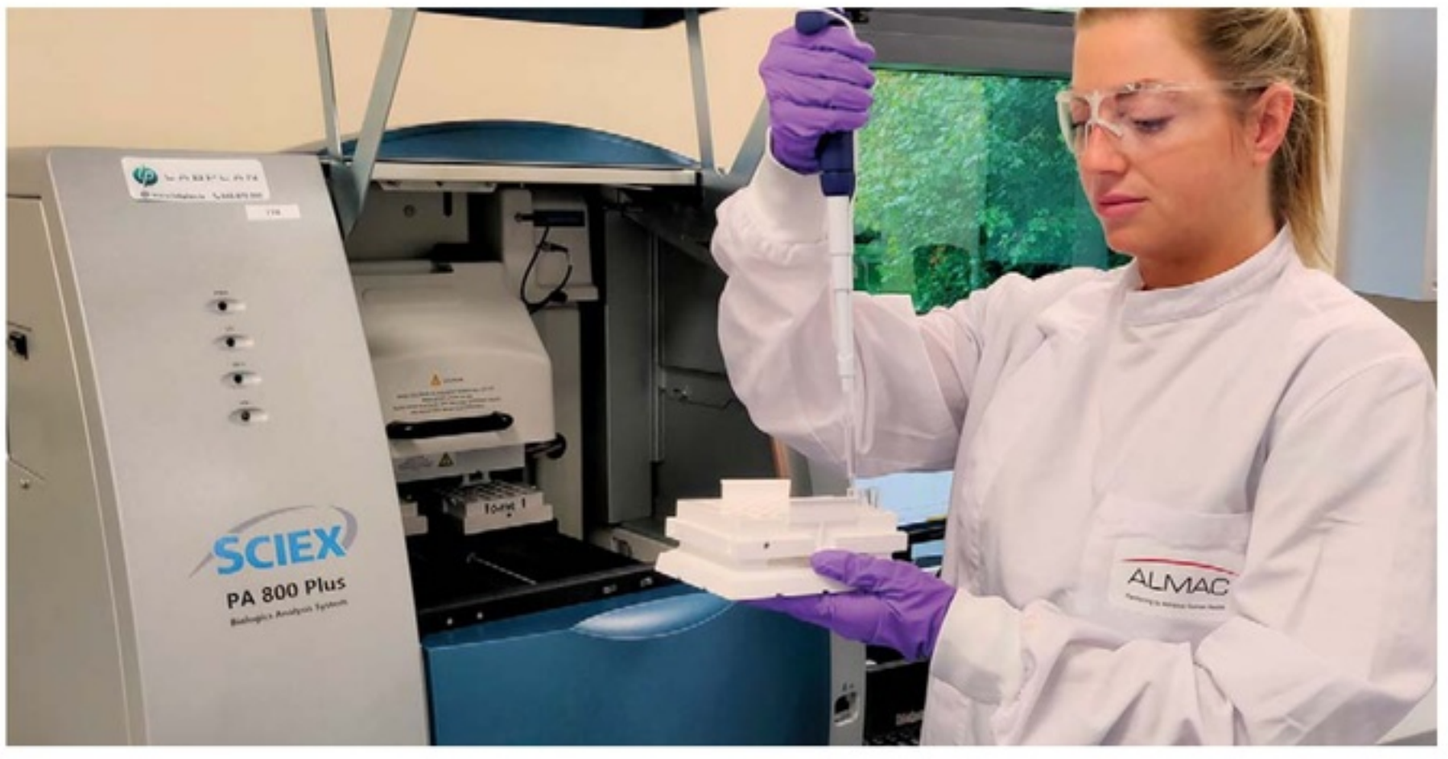
A Conversation with Almac Sciences

Cheryl Scott, with Pavan Kumar Kunala

Almac Sciences (a member of the Almac Group) recently expanded its suite of analytical solutions to include biologics testing. This follows a 2019 expansion of the company's facility in Athlone, Ireland, where it provides a comprehensive range of flexible pharmaceutical testing services to support drug development programs adhering to industry regulations and good manufacturing practice (GMP) standards.

"Biologics have gained huge traction in the past decade and are poised for stronger growth in the coming years with potential to significantly impact patient lives," says John Robson, Almac's vice president of analytical operations. "The launch of this service offering further demonstrates Almac's commitment to offering a best-in-class service to our global client base and advancing human health."

I spoke with Pavan Kumar Kunala (biopharmaceutical laboratory manager) about the expansion and some analytical trends in the industry.



Service Expansion

Tell us about the new services Almac is offering at its Irish facility. What major market trends led the company to this expansion? The healthcare industry has observed tremendous growth and diversification of biologics in the past decade. In 2019, 40% of drugs in the R&D pipeline were biologics, compared with 25% in 2009. Seven of the top 10 drugs by sales are monoclonal antibodies (MAbs). Increased investment in biologics R&D and commercialization is guiding many biopharmaceutical companies to outsource their development and manufacturing needs.

By outsourcing to contract organizations such as Almac, a growing biopharmaceutical company can move programs quickly toward clinical trials or commercialization without having to invest limited internal resources into scientists, equipment, and facilities. The advantage of outsourced analytical testing is the ability to leverage our technical expertise, access our state-of-the-art equipment, and take advantage of our platform methods already in place.

To meet the rising demand, we are now offering services for GMP lot release and stability testing, method development and validation, and raw material (RM) testing for biologics at Almac's Irish facility.

Raw Material Strategy

How does your company apply risk analysis to raw material monitoring/control, and how can you help clients develop their control strategies? RMs are critical components in biologics manufacturing and include solvents, resins, media, and excipients intended for use in production of both drug substances and drug products. Developers face several challenges to maintaining consistent RM quality (e.g., reliability in suppliers and changes in their manufacturing processes). A lack of clear understanding about how different material attributes of RMs can affect product quality adds complexity to the overall RM control strategy, as does the need to perform additional testing beyond pharmacopeial requirements.

At Almac, we understand that a higher degree of control is required for attributes that pose a higher risk to product quality and patient safety. For example, lot-to-lot variability of trace metals in cell culture media can affect protein glycosylation significantly, so trending of data is critical for ensuring consistent product quality.

RMs require clear and robust control strategies in order to assure their quality. A tier-based risk assessment usually is performed based on the phase of product development. The highest criticality is applied to RMs used in manufacturing drug-product materials; the next tier is for RMs used in drug-substance bioprocessing, followed by lower-tier RMs. At Almac, we help clients connect those dots and establish appropriate risk-based control strategies to ensure the quality and reproducibility of RMs through analytical testing, as recommended by

a 2018 concept paper from European Biopharmaceutical Enterprises (**3**).

Stability Testing

What are the main limitations of accelerated stability testing that can be addressed only through long-term studies? Biologics are inherently complex molecules that can undergo chemical and structural degradation, often requiring multiple orthogonal analytical methods to ensure their quality, safety, and efficacy. Stability testing is an integral part of product development to demonstrate that critical quality attributes (CQAs) remain unchanged throughout the proposed shelf life. It is important to understand the potential degradation pathways for a biologic, and accelerated stability studies help us quickly predict those degradation kinetics using an Arrhenius model.

However, the degradation pattern observed for biologics in accelerated stability conditions may not always be predictive of long-term conditions. For example, polysorbates are widely used as surfactants in biologics formulation, but they can undergo autooxidation at elevated temperatures and cause oxidation of a biologic. Such changes may not be reflected in long-term stability conditions. Therefore, stability trends obtained with accelerated conditions always need to be substantiated with long-term stability data.

Almac offers comprehensive and cost-effective stability testing, study management, and stability storage services in accordance with current GMP and other guidelines. Our all-inclusive stability service encompasses protocol design, analytical method transfer, study management, sample analysis, and quality assurance (QA) reporting, taking into account transport simulation and in-use stability programs. Our UK, European, and US state-of-the-art, walk-in stability chambers provide 300 m^3 of climatic storage facilities to satisfy all requirements.

Biostatistics

How important are statisticians to biopharmaceutical analytical laboratories these days? Although the concept of quality by design (QbD) is well established in the biopharmaceutical industry, it is confined mainly to process development and manufacturing fields and less adopted for analytical methods. The latest ICH Q14 draft guidance encourages users to develop robust analytical methods based on QbD principles. That includes determination of design space through statistically based design of experiments (DoE) and a comprehensive and quantitative assessment of each analytical method. The QbD approach is useful particularly for complex and variable analytical methods such as bioassays and high-performance liquid chromatography (HPLC) and helps immensely during lifecycle management.

All that requires significant input from statisticians to develop structured DoE and interpret results. Statisticians also play an important role in setting release and stability specifications, demonstration of biosimilarity, and trending data through control charts. Overall, analytical laboratories are more dependent on statisticians now than ever before, and this trend is on the rise.

We have the internal expertise and tools required to work by QbD principles when our clients require it. We recognize the increased importance playing such a role dictates within analytical laboratories and are confident that this approach will help our clients succeed in reaching their biological clinical milestones.

Analytical Method Transfer

How do you address analytical method transfer as part of planning? The recent rise in biologics approvals has led to increased activity in analytical method transfers within the biopharmaceutical industry. Typically, analytical methods are transferred during product development and postlicensure, either between laboratories in the same organization or to external contract analytical laboratories. Regulators expect every method transfer exercise to be robust and not compromise drug safety and efficacy.

Although method transfer is routine, it requires a significant amount of planning, preparation, and appropriate risk assessments for success. Considerations include selection of samples and reference materials, inclusion of stability samples, setting of transfer acceptance criteria, and determination of transfer type (comparative testing or covalidation). To provide robust evidence of reliable method performance, it is important to test a sufficient number of product lots at both the sending and the receiving laboratories. If an analytical method is stability indicating, then it is essential to test stability samples or forced-degradation samples to demonstrate that the method is sensitive enough to recognize changes in a drug product over its proposed shelf life. Transfer protocols also should include risk assessments and predetermined acceptance criteria.

Here, risk assessment includes the type of method being transferred — e.g., identity, purity, potency — and the type of transfer as well as past method performance, differences in instrumentation, and procedural modifications, if any. Acceptance criteria should be set based on historical method performance and data from stability and release testing. The range should not be set too wide or too narrow and should be determined carefully using a statistical approach.

Reference

1 Lloyd I. Pharma R&D Annual Review 2019. Pharma Intelligence 2019; https://pharmaintelligence.informa.com/resources/product-content/pharma-rnd-annual-review-2019.

2 Urquhart L. Top companies and drugs by sales in 2019. *Nature Rev. Drug Disc.* 19(228) 2020; https://www.nature.com/articles/d41573-020-00047-7.

3 *EBE Concept Paper: Management and Control of Raw Materials Used in the Manufacture of Biological Medicinal Products and ATMPs*. European Biopharmaceutical Enterprises: Brussels, Belgium, 17 December 2018; https://www.ebe-biopharma.eu/wp-content/uploads/2018/12/EBE-Concept-Paper-Raw-materials-version-2_final-draft_2018.12.17.pdf.

For more information, contact ***Pavan Kumar Kunala,*** *Almac's biopharma manager, at pavan.kumarkunala@almacgroup.com.*