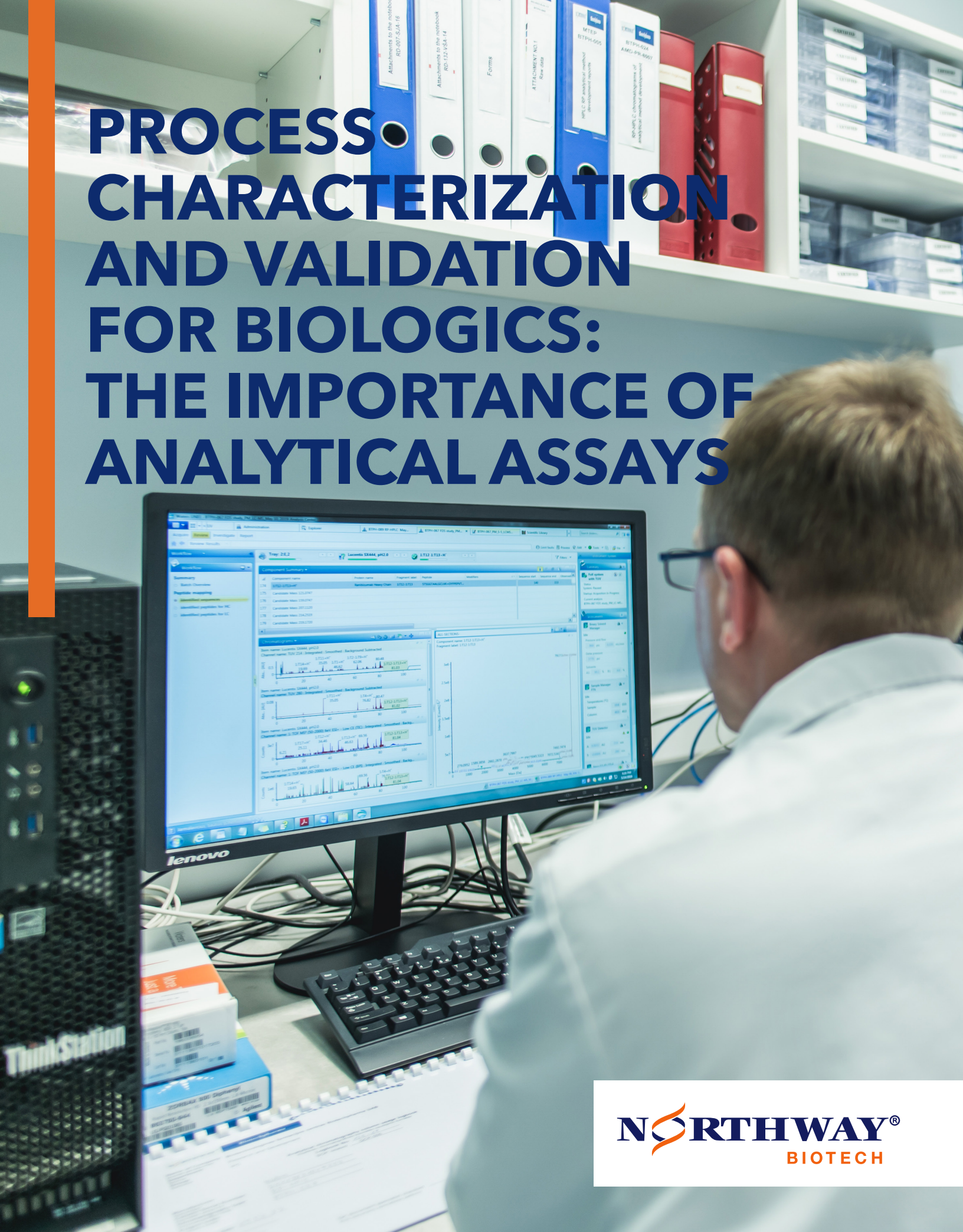
PROCESS CHARACTERIZATION AND VALIDATION FOR BIOLOGICS: THE IMPORTANCE OF ANALYTICAL ASSAYS



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PROCESS CHARACTERIZATION AND VALIDATION FOR BIOLOGICS: THE IMPORTANCE OF ANALYTICAL ASSAYS

By Vladas Algirdas Bumelis, founder and CEO, Dominic Chow, senior director of process development, and Gytis Miliauskas, head of chromatography method group, Northway Biotech

Analytical assays are an integral part of the drug development process, providing critical data to support the safety and efficacy of pharmaceuticals. While nearly every drug developer understands the importance of solid analytical capabilities in aggregate, recognizing the increased complexity of biologic analyses when compared to small molecule drugs can help companies new to the biologics space avoid unnecessary complications and prevent cost overruns.

There are a number of technologies and methods contract development and manufacturing organizations (CDMOs) employ to optimize a biologic's critical quality attributes. Ensuring a CDMO has the right analytical capabilities in place to deal with the increased complexity of biologic development is paramount. This vetting process hinges on a few key attributes: the experience of the CDMO, the depth and breadth of its analytical capabilities, and the degree to which its workflows are integrated across those analytical capabilities.

BIOLOGIC VS. SMALL MOLECULE DEVELOPMENT

In traditional small molecule analysis, a laboratory's analytical capabilities are employed to evaluate the primary structure and degradation pathway of the molecule. However, in biologic development, this analysis is much more intricate, as the molecules involved possess secondary and tertiary structures, creating added layers of complexity. As a consequence, maintaining the stability of a protein produced by cells during analytical development can be challenging. Many proteins can prove unstable under certain conditions, in contrast to the more simplified structure and comparative stability of small molecule drugs.

While there is overlap in the analytical methods used to evaluate small molecules and biologics, there are several key differences, particularly in purity and degradation testing. Because these are complex proteins with specific sequences, additional testing is required to determine the potency of the drug, the time it takes to degrade, and its overall safety and quality.

These factors all translate to a lengthier timeline for analytical assay qualification, characterization, and validation – typically, the process takes between four and six months, compared to the traditional two-to-three month timeframe seen in

small molecule development. This is in part because even one misstep in the process can result in severe delays: for example, small changes in process parameters during the fermentation and cell culture (for example, pH, oxygen, and raw materials) can lead to differences in the product quality and batch performance, necessitating reprocessing that can take months.

One of the best ways to reduce uncertainty and prevent time delays during the analytical assay process is by increasing the range of analytical methods used to evaluate a biologic. UV-Vis spectroscopy, ultra-high performance liquid chromatography (UPLC), high-pressure liquid chromatography (HPLC), mass spectrometry – the more tools a CDMO has at its disposal, the more likely it is to pinpoint and mitigate issues early in development. A batch of cells infected with mycoplasm can in turn put production batches at serious risk if a CDMO doesn't employ sufficient analytical capabilities to test for the quality of cell bank vials during the development process. Ultimately, every part of the process has implications further down the line, and thorough, varied testing is the first line of defense in avoiding issues that can derail a project.

There are also several challenges to establishing analytical methods with a high level of sensitivity. Because each method has its own drawbacks, unexpected complications can sometimes occur, and CDMOs must get creative in determining the best ways to gauge potency, determine stability, and measure concentration for certain biologics.

THE IMPACT OF DEVELOPMENT PHASE ON ANALYTICAL APPROACHES

The depth and breadth of a CDMO's analytical capability also become important when you consider the stage of a project. In the earliest phases of a project, the primary focus is on analytical method development. Later in clinical development, that focus shifts to process characterization and process validation, and chosen analytical methods are qualified to ensure they will work robustly within different buffer matrices and for various in-process control parameters. Once the analytical methods for the project have been validated, the CDMO employs them as part of its late-phase testing and eventual commercialization.

For CDMOs with fewer analytical methods at their disposal, performing end-to-end development on a project becomes a difficult proposition. This typically forces companies to look for additional CDMO partners to fill gaps in later stages of a project, creating a scenario wherein multiple CDMOs are asked to collaborate or transition work. While the potential for this outsourcing varies, depending on the complexity of the project itself, contracting with a CDMO that can minimize its own outsourcing need through proactive equipment and facilities investment can profoundly simplify the process.

But for those companies that require a CDMO to transition onto a project in later development stages, it is important that they approach the process with realistic expectations and a collaborative mindset. Things like differences in the equipment utilized between CDMOs can impact the results of analytical testing. For example, variations in the materials used between CDMOs can also play a part in creating testing variances. Some materials may only be supplied in certain countries or regions, or a previous CDMO partner may have utilized older or outdated equipment for part of its process. These factors represent challenges that fall to the later-stage CDMO to solve, making open communication on the part of the CDMO and company integral to building a workflow and plan that will carry the project to fruition.

Ultimately, the purpose of a CDMO is simple: it provides the capabilities, expertise, equipment, and facilities that represent an undue capital expenditure burden for companies. In order to optimize its utility to the companies it partners with, then, a CDMO should look toward continuous investment in its analytical methods, equipment, and facilities. This often includes investment in duplicative equipment; having multiple models of the same piece of equipment allows a CDMO to accept more projects without delays and perform different projects to the same standard.

CHOOSING THE RIGHT FIT

Once a company has established a CDMO possesses the necessary analytical capabilities, it must then determine if the CDMO has the right workflows and protocols to streamline processes and protect proprietary product information. Data integrity is one of the key considerations for companies in biopharmaceuticals, a hyper-competitive space with a slew of

regulatory standards. At Northway Biotech, our approach to data integrity and process development is modeled after good laboratory practice (GLP) standards and also leveraged from our good manufacturing practice (GMP) facilities. This blended approach ensures data is secured from a custody standpoint, as well as for data tracing and sample tracking purposes.

Another important intangible is experience. Northway Biotech has 16 years of experience working with dozens of companies and has built a team of more than 150 laboratory specialists across our two sites in Lithuania and Massachusetts. This experience has also resulted in more than 8,000 documents, including SOPs, agreements, and other process-related documents that allow for template building, process improvement, and accessible institutional knowledge to help our partners. In addition, Northway Biotech's experience, spanning more than 100 projects, covers a wide range of biomolecules, from monoclonal antibodies to therapeutic proteins including enzymes and fusion proteins.

These approaches are all complemented by Northway Biotech's investment in state-of-the-art facilities and equipment. Northway Biotech's analytical capabilities include:

- liquid chromatography (SEC, RP, IE, and HIC HPLC) analytical method development, qualification and validation
- development, qualification, and validation of capillary gel electrophoresis, icIEF, SDS-PAGE and other protein purity methods
- analysis by UV-Vis spectroscopy, ELISA, Octet, RT-PCR and Biacore
- subvisible particle analysis by compendial light obscuration and MFI methods
- elucidation of protein structure by LC-MS/MS
- development, qualification and validation of cell-based biological assays

CONCLUSION

Analytical development and further testing of manufactured drugs are crucial components in ensuring their quality and safety. In order to stay competitive, companies should seek to partner with CDMOs that have a proven track record in developing analytical assays for process qualification, characterization, and validation. These companies must also recognize the increased complexity inherent to performing analytical testing on biologics, as well as what to look for in a CDMO in terms of both analytical capability and other intangible factors. Finally, companies looking to outsource their manufacturing, either from the outset of a project or midstream, should consider what they need to bring to the table from a communication and data sharing standpoint to maximize their chances of success.

ABOUT THE AUTHORS

Vladas Algirdas Bumelis, Prof., is the Founder and CEO of Northway Biotech. He holds PhDs in both chemistry and biotechnology from Vilnius University and is a full member of the Lithuanian Academy of Sciences. Prof. V. Bumelis has extensive experience in the pharmaceutical and biotech industries, having previously served in senior management positions at international companies in the biopharma industry such as Teva Pharmaceuticals, Sicor Inc., Biofa, and Biotechna. His illustrious career has been recognized many times. In 2004, Prof. V. Bumelis received the Science Award of Lithuania in recognition of his achievements in the development and production of recombinant proteins, while in 2012, he was named CEO of the year in Lithuania. Vladas can be contacted at vladas.bumelis@northwaybiotech.com.

Dominic Chow, PhD, is the Sr. Director of Process Development for Northway Biotech's site in Waltham, MA. Dominic has more than 15 years of experience in the biotechnology and biopharmaceutical industry. He specializes in process development and characterization, technology transfer, scale-up, and manufacturing support for biologics (monoclonal antibodies, enzymes, and recombinant proteins) and novel therapeutics (antibody drug conjugates and mRNAs). He previously worked for Lonza Biologics, Bristol-Myers Squibb, ImmunoGen, and Moderna. Dominic has an MSc and a PhD, both in chemical engineering, from Northwestern University, and conducted his post-doc in biomedical engineering at Duke University. He can be contacted at dominic.chow@northwaybiotech.com.

Gytis Miliauskas, MSc, is the Head of the Chromatography Method Group for Northway Biotech. Gytis has worked in biotechnology for nearly seven years; he began his career as a junior biotechnologist in Thermo Fisher Scientific before becoming a scientist in R&D. In that role, he was responsible for supporting manufacturing by specializing in troubleshooting problems unresolved by retesting, and for facilitating technology transfer for different sites. In the year prior to joining Northway Biotech, Gytis also served as a project coordinator, which offered him a more holistic understanding of client needs, communication, and workflows. Gytis possesses practical and theoretical knowledge regarding many different types of assays, from bioassays such as PCR, RT-PCR, and ELISA, to physicochemical assays, including UV, electrophoresis, and chromatography.

ABOUT NORTHWAY BIOTECH

Northway Biotech is a leading CDMO supporting customers worldwide. Its highly experienced, professional team executes projects at any stage, from cell line construction and process development to cGMP manufacturing of biopharmaceutical products. The company's wide-ranging expertise and vertically integrated service offerings translate to the ability to rapidly execute multiple projects from its state-of-the-art GMP facilities, while ensuring full process and product compliance at all stages of research, development, and commercial manufacturing. Northway Biotech is a privately owned company founded in 2004 and located in Vilnius (Lithuania) and Waltham, MA (USA).

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