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Advancing QC Efficiency with SEC-MALS System and Empower Software

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INTRODUCTION

The structure-function relationship is fundamental to the efficacy and safety of biotherapeutics. Maintaining proper protein conformation ensures stability and function while reducing aggregation that may trigger unwanted immune responses. Physical triggers such as air-liquid interfaces, agitation, and even light exposure are all events that can induce self-association. To ensure product quality, the identity and quantity of oligomers and other high molecular weight species (HMWS) must be closely monitored throughout GxP-compliant development and in quality control (QC).

Size-exclusion chromatography coupled with multi-angle light scattering (SEC-MALS) is an ideal technique for this purpose. Unlike traditional chromatography, which relies on retention time and column calibration, SEC-MALS directly measures the absolute molar mass of proteins and peptides, confirming their identity and oligomeric state with high accuracy. This technique is particularly advantageous as it does not require additional acquisition time, operating downstream of a UV detector and utilizing the same high-performance liquid chromatography (HPLC) system already in use.

BRIDGING SEC-MALS PRECISION WITH ENTERPRISE-WIDE COMPLIANCE

Waters™ Empower™ Chromatography Data System (CDS) is the first platform to seamlessly connect enterprise-wide workflows with integrated MALS data acquisition and analysis capabilities.

Empower Software users now have access to the world's most advanced MALS instruments from Wyatt Technology™, including the DAWN™ and miniDAWN™, equipping laboratories with essential capabilities critical to reducing risk in development and QC, while enabling product quality and patient safety. The DAWN MALS instrument line offers the highest sensitivity and the broadest molecular weight range.

By combining the precision of SEC-MALS with enterprise-level connectivity, Empower Software represents a significant advancement in biotherapeutic analysis, streamlining GxP and QC workflows within a validation-ready ecosystem designed to keep pace with evolving regulatory and scientific demands.

SEC-MALS INCORPORATION INTO GXP LABS AND QC PROCESSES

The adoption of SEC-MALS in GxP labs and QC processes is driven by the need for enhanced safety and more precise measurements. Traditional SEC-HPLC methods rely on elution time and calibration standards to determine molar mass. However, elution time can be affected by factors such as column temperature, mobile phase variability, column aging, instrument differences, and analyst handling, introducing bias and inaccuracies. In contrast, MALS directly determines molar mass from first principles, eliminating reliance on calibration standards that may not accurately represent the molecules of interest and reducing uncertainties inherent in traditional techniques.

Figure 1. Example SEC-MALS configuration: The DAWN MALS instrument and Optilab™ differential refractive index (dRI) detector coupled to an Arc™ Premier System. Empower CDS provides seamless operation, analysis, and audit trails.

Combining Empower Software with MALS simplifies hardware and workflow integration for routine analysis, making MALS an accessible detection technique for chromatographers. The MALS detector is positioned downstream of a UV detector, utilizing the same HPLC system already in use in the SEC-HPLC setup. Once integrated, MALS data are collected simultaneously during routine SEC-HPLC experiments, delivering complete and reliable analysis. Its ease of use and QC readiness are essential for seamless integration into regulated workflows.

CASE STUDY: PLATFORM SEC-MALS FOR MABS

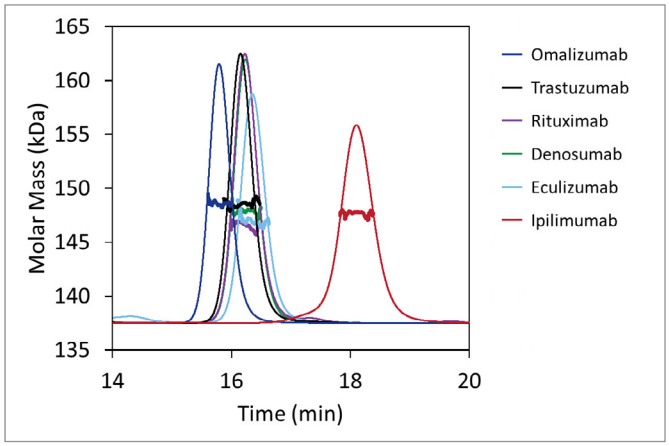

Figure 2. Elution time variability across different mAbs. MALS provides accurate molar mass regardless of elution time and simplifies method development and transfer across sites.

SEC-MALS is a powerful platform method for size variant analysis. For example, ipilimumab and omalizumab exhibit significant elution time deviations, which can be misinterpreted as aggregates or fragments. By directly determining absolute molar mass without relying on elution time, SEC-MALS eliminates uncertainty in identity. The same method can then be applied across different samples and analyzed with confidence.

CASE STUDY: SIZE-VARIANT ANALYSIS

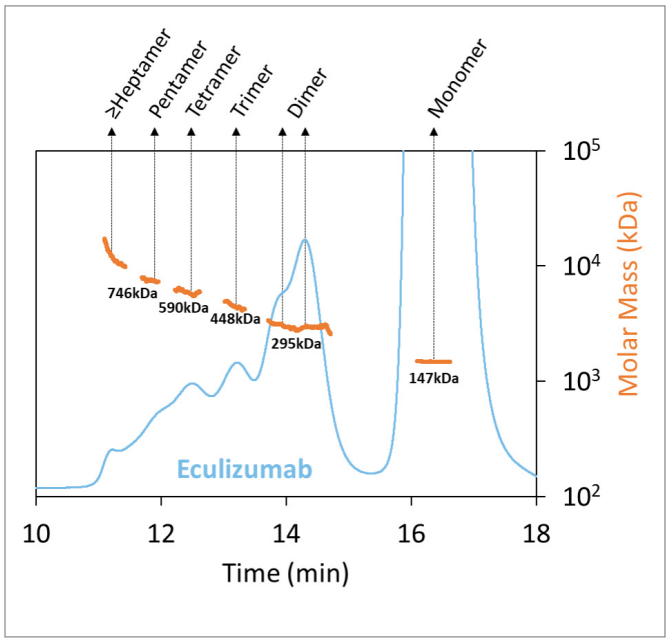

Figure 3. SEC-MALS analysis of aged eculizumab reveals a complex distribution of HMWS. Absolute molar mass values obtained from MALS enable confident identification of the nature of the aggregates.

SEC-MALS can accurately identify aggregates and oligomers by measuring absolute molar mass. For example, in this aged eculizumab sample (Figure 3), SEC-MALS revealed a complex distribution of aggregates and successfully determined the molar masses of various HMWS peaks. Additionally, light scattering detectors offer higher sensitivity to aggregates than UV detection, ensuring more consistent peak identification.

CASE STUDY: BIOSIMILAR ASSESSMENT

SEC-MALS is routinely used as part of an analytical panel to enable direct comparison between biosimilars and reference biologics, verifying structural similarity and ensuring the biosimilar meets regulatory safety and efficacy requirements.

CASE STUDY: FORCED DEGRADATION

The importance of stability testing is outlined in the International Council for Harmonization (ICH) guidelines, including Q5C, Q6B, and Q1B, which provide a framework for assessing the stability of biotechnological and biological products during processing, shipping, and storage. SEC-MALS plays a crucial role in this process by accurately measuring molar mass and helping to identify and characterize aggregate formation, product-related impurities, and changes in higher-order structure caused by thermal, chemical stress, or mechanical agitation. The incorporation of SEC-MALS for stability testing helps to reduce potential risks to product quality and patient safety.

Degradation Type
Oxidation
Photolysis
Thermal Stress
Hydrolysis
Mechanical Agitation

Table 1. A list of typical forced degradation studies that assess drug stability, identify degradation pathways, and guide manufacturing and storage controls.

BENEFITS OF EMPOWER CDS FOR MALS QC AND GXP ADOPTION

Empower CDS streamlines data acquisition, management, processing, and reporting. It scales from a single workstation to an enterprise-wide network, enabling regulatory compliance and the simplified adoption of advanced instruments in GxP and QC labs.

- **Reduce risk with instrument control**: Easily manage both liquid chromatography (LC) and MALS digitally to avoid skipped injections and ensure peak alignment.
- **Increase productivity with streamlined data analysis**: Save time and reduce manual integration for more precise peak analysis, minimizing errors associated with manual methods.
- **Increase efficiency with centralized data management**: Simplify data retrieval and storage, while reducing the risk of errors and ensuring consistency across the lab.
- **Maximize investments with scalability**: Flexible deployment options allow labs to expand from a single workstation to a global enterprise-wide system leveraging on-premises, datacenter, or cloud infrastructure.
- **Reduce cost with consolidation**: Integrating MALS with Empower Software reduces the overall costs associated with maintaining multiple software systems.

Empower Software with SEC-MALS analysis results in a significant reduction in effort across the entire organization, streamlining scientist workflows, data management, and audit readiness.

CONCLUSION

Empower CDS is the first software to seamlessly integrate enterprise-wide workflows with SEC-MALS instrument acquisition and analysis capabilities. By combining the precision of SEC-MALS with enterprise-level connectivity, Empower Software represents a significant advancement in biotherapeutic analysis. It produces high-quality data while reducing effort for scientists, simplifying IT validation, and improving audit readiness. Empower CDS streamlines GxP lab and QC workflows within a validated ecosystem that adapts to evolving regulatory and scientific demands, ensuring the production of high-quality therapies.

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