The Importance of Mass Spectrometry

Mass spectrometry (MS) has long been a cornerstone analytical technique in the pharmaceutical and biopharmaceutical industries. Its ability to provide detailed molecular information has made it indispensable in the development, characterisation, and quality control of complex biological products. As the landscape of therapeutics evolves to include biologics, cell and gene therapies, and nucleic acid-based treatments, MS continues to adapt, offering solutions to emerging analytical challenges.

For those seeking a deeper technical insight into this topic, my colleague, Dr. Milena Quaglia, has written a comprehensive review article on the evolution of mass spectrometry for the analysis of bioproducts, which is available on the RSSL website. Readers are encouraged to refer to that article for more detailed discussion and reference information.

Biopharmaceutical Foundations
Traditional biologics, such as monoclonal antibodies (mAbs), remain a critical part of pharmaceutical pipelines. Characterisation of these large and heterogeneous molecules requires detailed structural information to confirm identity, assess post translational modifications, and evaluate stability. MS plays a pivotal role here through peptide mapping, intact mass analysis, and glycan profiling.

MS based methods offer unparalleled resolution and accuracy when assessing changes to mAbs over time or in response to formulation conditions. Moreover, regulatory guidance from agencies such as the FDA and EMA increasingly expects high resolution analytical data during product development. As such, MS provides not only research support but also fulfils critical roles in meeting compliance and quality expectations.

Cell and Gene Therapy
Cell and gene therapies (CGTs) represent some of the most innovative and complex modalities currently in clinical development and commercial use. These therapies rely on delivering genetic material to modify or correct cellular function. Viral vectors, such as adeno associated viruses (AAVs), are among the most common delivery vehicles.

One of the key analytical challenges in this space is the characterisation of viral vector particles; specifically, understanding the ratio of full to empty capsids, detecting aggregates, and confirming identity. While techniques such as qPCR and ELISA are commonly used, MS is emerging as a powerful complementary tool.

Native MS allows the analysis of intact AAV capsids in their natural, non-denatured form. This technique offers insights into capsid assembly, particle integrity, and batch heterogeneity. When combined with ion mobility spectrometry, it can provide data on size and conformation, offering a deeper understanding of the structural landscape of viral vectors.

Additionally, proteomic workflows can be used to characterise the proteins making up viral capsids or the host cell protein (HCP) impurities that may co-purify during production. Given the immunogenic risk posed by HCPs, their detection and quantification are essential. MS based proteomics, including data independent acquisition (DIA) and parallel reaction monitoring (PRM), provides sensitive and specific options for profiling these impurities.

Characterisation of Gene Therapy Components
In gene therapies using plasmids or mRNA, another layer of complexity is introduced. Mass spectrometry can contribute to the characterisation of nucleic acid structures and assess degradation products. Although MS of large RNA molecules presents challenges due to size and ionisation efficiency, progress is being made in the use of top-down and bottom-up strategies to identify sequence integrity and chemical modifications.

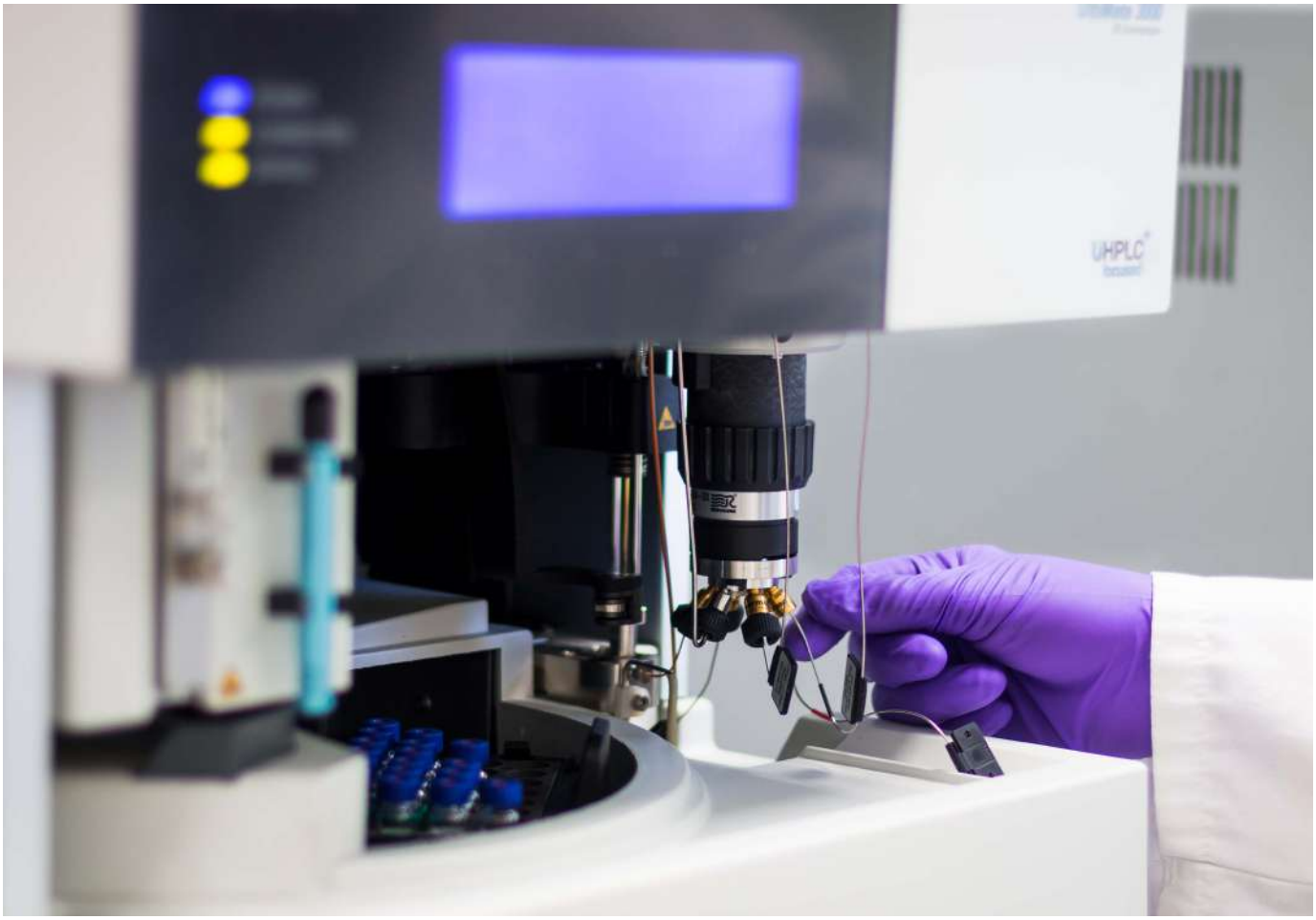
Lipid nanoparticles (LNPs), which are increasingly used as delivery systems from RNA therapies, also require detailed compositional analysis. MS can be employed to study the lipid components, identify impurities, and ensure batch to batch consistency, especially when combined with chromatography-based separations.

Advanced Instrumentation and Workflows
The evolution of instrumentation has significantly expanded the capabilities of MS. High resolution accurate mass (HRAM) systems, such as Orbitrap and time of flight (TOF) analysers, are now standard in many labs due to their sensitivity and resolution. Coupling these instruments with ultra-high performance liquid chromatography (UHPLC) or capillary electrophoresis (CE) provides powerful multidimensional analytical platforms.

Ion mobility spectrometry (IMS) adds a further separation dimension based on molecular shape and size, which is particularly useful when analysing conformers or aggregates. When applied to biotherapeutics or viral vectors, IMS-MS workflows can uncover hidden heterogeneity and identify minor variants that may impact safety or efficacy.

The adoption of automation and data processing software also continues to improve, facilitating high throughput workflows, minimising human error, and improving data reproducibility. These developments are critical in CGT pipelines, where speed to market can be a competitive differentiator.

From Discovery to QC
Initially, MS was primarily a tool for discovery and development.



However, its role in quality control (QC) is growing. With improvements in robustness and user-friendly software, MS based methods are now being validated for lot release testing. In CGTs, where conventional methods may not suffice, MS offers precise identification and quantitation capabilities suitable for QC environments.

Regulatory acceptance is increasing, particularly when MS methods are shown to offer advantages over traditional techniques. As such, companies are investing in the development of platform MS methods that can be adapted across a range of products.

Outlook and Challenges

Despite its advantages, the integration of MS into routine workflows in CGT is not without obstacles. Challenges include the complexity of sample preparation, especially for cell-based therapies, and the need for standardised protocols. Instrument cost and the requirement for skilled operators can also be limiting factors for smaller organisations or early-stage developers. Nonetheless, ongoing advances in miniaturisation, automation, and data interpretation are likely to mitigate these issues. Cross industry initiatives aimed at harmonising analytical standards are also expected to support broader adoption. The push toward digital transformation in pharma and biopharma is likely to further embed MS into data driven decision making. The ability of MS to provide comprehensive, high resolution molecular information positions it as a cornerstone technology not just for traditional biologics but also for next generation therapies.

Conclusion

Mass spectrometry is no longer just a research tool; it is rapidly becoming a critical enabler of modern medicine. From the detailed characterisation of biologics to the emerging applications in gene therapy and viral vector analysis, MS provides unmatched analytical power. As therapeutic modalities continue to diversify, the role of MS will only grow, shaping the future of pharmaceutical development and quality control.

REFERENCES

1. https://www.rssl.com/insights/life-science-pharmaceuticals/the-evolution-of-mass-spectrometry-for-analysis-of-bio-products/

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