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Is the Multi-Attribute Method (MAM) the Next Big Thing? A High-Resolution Accurate Mass Multi-Attribute Method for Critical Quality Attribute Monitoring

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1. Introduction

The history of medical science is full of exciting technological advances. From antibiotics deemed "wonder drugs" in 1929 to the discovery of DNA's double helix by James Watson and Francis Crick in 1953, we have seen huge scientific advances as an outcome of and response to massive global health challenges. Is the Multi-Attribute Method (MAM) next in line to be one of the greatest technical developments of the healthcare industry in this decade -- reducing the frequency and severity of immense manufacturing challenges of the biopharmaceutical industry?

The biopharmaceutical market has grown rapidly over the past few decades due to increased demand and the promise of biotherapeutics treating life-threatening diseases. More and more companies are becoming active in developing both innovator products and biosimilars. But, unlike small molecules, protein biotherapeutics are quite complex, containing molecular heterogeneity caused by post-translational modifications, higher-order structural changes, and aggregation. All these characteristics may contribute to the safety and efficacy profile of the biopharmaceutical and therefore must be characterized and monitored from drug discovery through quality control in manufacturing.

Over the past several decades, the structural complexity challenges of characterizing biotherapeutics have been largely addressed with a variety of analytical methods that must often be used orthogonally. However, the streamline of analytics is becoming necessary because of the increased need for deeper product and process understanding driven by quality-by-design principles (QbD) and heightened time and cost pressures of biopharmaceutical manufacturing due to the sheer number of products coming through the development pipeline.

The MAM movement is a perfect example of where opportunities in science, driven by technological advances, meet industry necessity. MAM is based on LC-MS peptide mapping techniques, typically using high-resolution mass spectrometry to acquire high resolution and high accuracy mass data. As the technique has progressed over the years, the focus has turned to automation and software development to allow for automated identification and quantitative analysis of each molecular attribute. With automation and software developments, a true benefit of MAM can be realized by building a comprehensive molecular attribute database linked to process conditions which can then be used to increase product and process knowledge throughout the development pipeline. With this increased product and process knowledge, MAM can reduce the amount of time taken to develop a product, reduce the time needed to manufacture and release a product by adding efficient process controls, and reduce the time needed to investigate a process issue. MAM can help to solve major manufacturing challenges plaguing the biopharmaceutical industry today as they strive to develop more biotherapeutics on a faster timeline.

The aim of this work is to develop a high-resolution accurate mass (HRAM) multi-attribute method (MAM) for the analysis of monoclonal antibody (mAb) critical quality attributes (CQAs). We shall describe the optimization and application of the Multi- Attribute Method as a complete workflow to monitor CQAs of the NISTmAb standard, including glycosylation, deamidation, isomerization, succinimide formation, oxidation,

C-terminal lysine truncation, N-terminal pyroglutamate, and glycation, under normal and stressed conditions. In addition, we will demonstrate the capability of the HRAM MAM workflow for new peak detection (NPD) using spiked and stressed samples. The importance of HRAM in CQA quantitation and NPD will be discussed.

2. Results

The presented HRAM MAM workflow provides the robustness, flexibility, specificity, and sensitivity to not only identify PQAs and quantify multiple CQAs simultaneously, but also detect new features associated with changes induced by sample preparation, storage, and processing. The HRAM ability of the Orbitrap mass spectrometers make it possible to resolve species that would otherwise be overlapped, leading to accurate CQA quantitation and reliable NPD. This, combined with a very robust chromatographic separation produces reproducible results that can be confidently submitted for review by regulatory agencies.

Biopharma Finder software offers rapid peptide mapping, easy CQA selection, and accurate quantitation in a non-compliant environment. The seamless transition from BioPharma Finder software to universal Chromeleon chromatography and mass spectrometry software enables CQA quantitation and monitoring, as well as NPD, to be performed within a compliant GMP environment. This combination of software utilization provides flexibility in the different phases of drug development and release. It should be emphasized that Chromeleon software affords a comprehensive and fully realized GMP-compliant environment; from instrument configuration, calibration, and tuning through data acquisition, processing and reporting is fully audited with restricted user roles and signatory requirements.

As the MAM gains in popularity and recognition within the biopharmaceutical industry and with the regulatory agencies, the workflow described herein can serve as useful guidance for those who are using, or wish to use, this technology in different phases of drug development and QC.