Genedata
solutions in silico

Just
biotherapeutics for all

> ***We needed something that enabled higher throughputs than the vendor software package we were using, so we turned to Genedata Expressionist. We can give Expressionist hundreds of files, and it is able to process them in a very quick manner.***
>
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ABOUT JUST
Just Biotherapeutics is an integrated design company focused on technologies that will accelerate development of biotherapeutics and substantially reduce their manufacturing cost.

GENEDATA SOLUTION
EXPRESSIONIST

Automated Software-Driven MAM Implementation for Biotherapeutic Characterization

Background

Conventional biopharmaceutical characterization and quality-control methods are based on determination of physical attributes through classic biophysical analysis technologies that rely on indirect measurement of the molecules contained in the sample. Because biologics are heterogeneous mixtures of complex molecules, more advanced techniques that provide direct measurements of the attributes are desired. Recently, an alternative approach based on liquid chromatography-mass spectrometry (LC-MS) has been developed[1,2]. Termed the multi-attribute method (MAM), this approach uses the content-rich data provided by mass spectrometric analyses to characterize biopharmaceuticals at the molecular level.

The advantages of mass spectrometry are leveraged at two stages in the MAM approach (Figure 1 overleaf). First, LC-MS/MS is used to characterize biopharmaceuticals by identifying peptides, post-translational modifications, and clipping sites. Second, the integrity and heterogeneity of biotherapeutics are monitored by LC-MS to quantify critical quality attributes identified during characterization with the added advantage of detecting new and unexpected peaks (which correspond to impurities or contaminants).

Main Challenges

Increasing data processing throughput

A major challenge in analyzing biotherapeutics using mass-spectrometry-based methods is handling the large amount of data generated. Comprehensive in-depth characterization is a long and complex process, requiring frequent analysis of various samples, as well as large-scale studies. Because current solutions often rely on multiple software packages and manual transfer, data processing and analysis can represent a major bottleneck in the biopharmaceutical development process.

Reducing the number of false-positive identifications

While offering numerous advantages over electrophoretic and chromatographic assay data, the richness of MS data can lead to the generation of large numbers of false-positive identifications. False positives—such as incorrectly annotated in-source fragments—must be manually investigated, a process that is typically laborious and time-consuming.

Detecting new and unexpected peaks

MAM monitoring systems must deliver efficient, reproducible, and reliable detection of new or unexpected peaks. New peak detection is achieved by comparing a reference and sample base peak chromatogram. Often, software approaches base detection solely on predefined peak lists, and are consequently unable to detect and identify unexpected signals.

Collating, sharing, and leveraging knowledge

Development and manufacturing of biopharmaceutical molecules generates data from a multitude of sources. For example, during candidate development, expression vectors, cell lines, and bioreactor conditions must be monitored and optimized. Understanding how changes to these factors affect the biopharmaceutical product requires a data system that can manage and collate large amounts of disparate data that are often produced in different locations using different software packages.

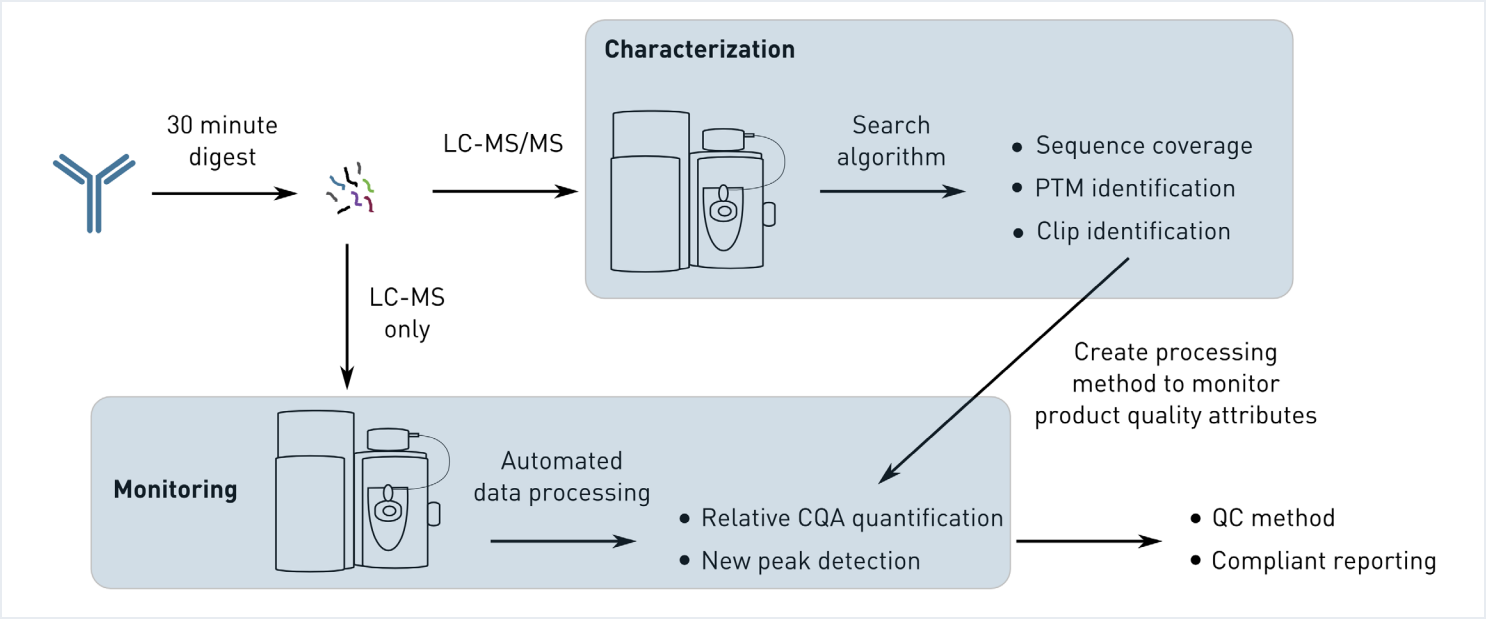
Providing compliant and flexible reporting

Reports should provide a transparent summary of product batch-to-batch consistency and meet the demands of both manufacturers and local regulatory bodies. When discovered, quality issues must be immediately communicated and ideally, potential causes should be able to be determined from a data trail.

Solution

Intelligent, automated MS data processing

Genedata Expressionist processes and analyzes data from any MS instrument using fully automatable and configurable workflows, in which data are subjected to sequential processing steps. Metadata can be used to directly apply specific parameters to individual data sets at any step; offering complete control over each experiment while boosting productivity by increasing throughput and eliminating laborious manual intervention.



1 *Schema demonstrating the MAM process used in characterization and quality-control monitoring of biopharmaceuticals. LC-MS: Liquid chromatography-mass spectrometry; CQA: Critical quality attribute; PTM: Post-translational modification; QC: Quality control.*

Intelligent filtering to limit false positives

Genedata Expressionist workflows are highly flexible and are designed to automate processes specific to each user. Each step of the workflow can be controlled by user-definable settings, offering an unparalleled level of control during MS data processing. For example, signals can be filtered according to their intensity, charge, or presence in a given proportion of samples. This provides an efficient method for reducing the number of false-positive identifications, while ensuring that genuine contaminants are not overlooked.

Advanced signal-driven new peak detection

Using Genedata Expressionist, after reference and sample data are compared and signals corresponding to expected species are filtered out, new peaks are automatically identified and quantitated using dynamic peak detection and clustering algorithms. Analysis can be performed on all data; including quantified CQAs, new peaks, known contaminants, and unannotated masses. Alternatively, the data can be filtered to focus analysis on the signals of interest.

Creating a molecular knowledge base that efficiently leverages all product information

As an enterprise software, Genedata Expressionist fully integrates into and across existing data systems and provides a sophisticated and scalable processing platform. Using the dedicated project management extension and a knowledge database enables product information generated in upstream processes (such as characterization) to be leveraged in downstream processes (such as monitoring) across entire organizations (Figure 2).

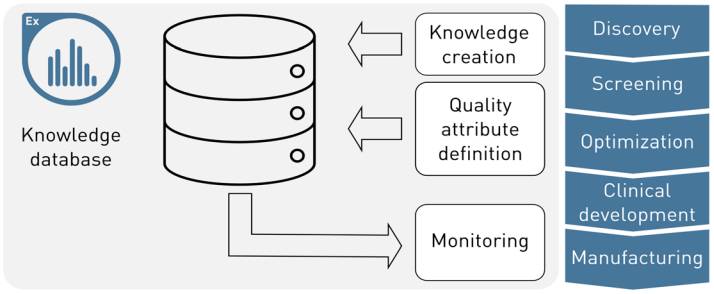
Configurable reporting during monitoring

Monitoring starts with a system suitability test, which ensures that the instrumentation is functioning correctly. After the trustworthiness of the data is confirmed, CQA monitoring and new peak detection are performed. Fully configurable reports can be produced at any stage, and users can be automatically notified in the event of any issues.

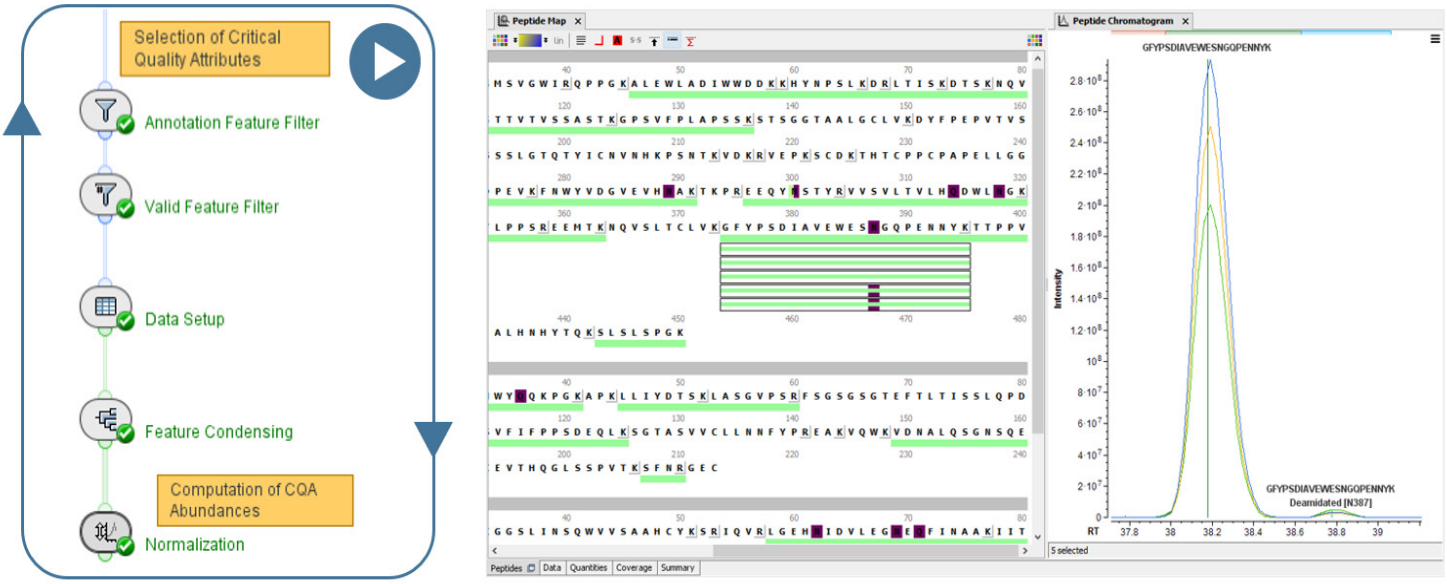
Benefits

Increased productivity

Using optimized Genedata Expressionist workflows, data processing for MAM monitoring can be fully automated, enabling processing of hundreds of samples per week with very little manual interaction. By eliminating potentially error-inducing manual steps, automated data processing and reporting significantly streamline MAM monitoring and greatly increase productivity and the level of confidence in the quality of the data.



❷ *Leveraging knowledge gained during development for MAM monitoring*



❸ *Annotated CQA identification and quantitation in MAM monitoring*

Easier collaboration and better decision-making
The enterprise nature of Genedata Expressionist facilitates knowledge transfer and harmonizes processes within and between labs and provides every user within an organization with fast and easy access to all relevant knowledge on a given biopharmaceutical, thereby allowing full leveraging of content-rich MS data in decision-making.

Less time required for data review and triage
Knowledge-based grouping and filtering of spurious signals greatly reduces the number of false-positive signals and consequently the time required for data review and curation.

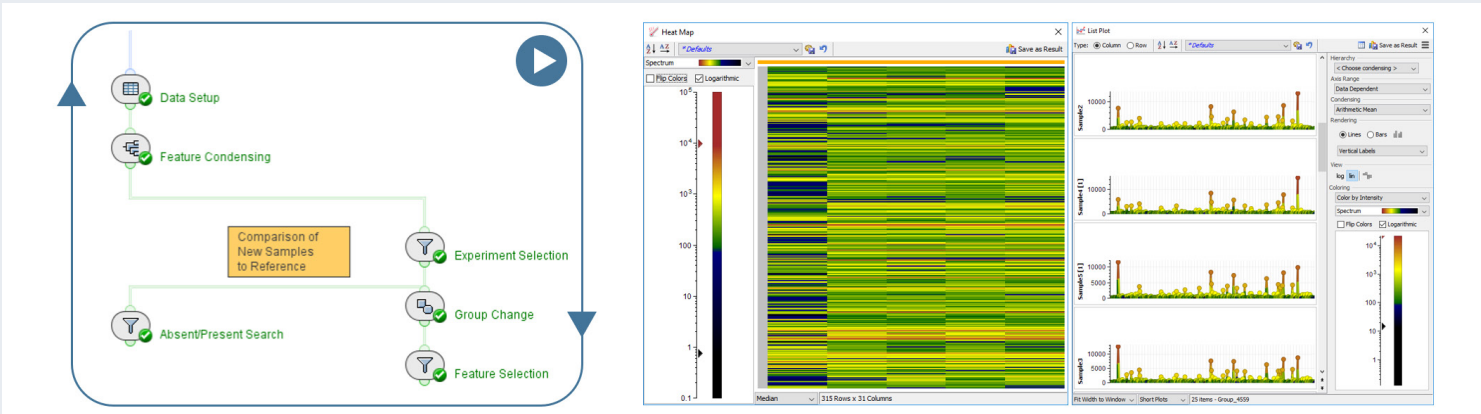
Intuitive, dynamic reporting enabling fast responses
The highly configurable reporting functionalities that are part of Genedata Expressionist can provide intuitive overviews of all stages of data processing.

Automatic notifications can alert users to the presence and source of quality issues as soon as they arise.

Efficient detection of new and unexpected peaks
In contrast to approaches that rely solely on predefined peak lists, Genedata Expressionist takes all available MS data into account during MAM new peak detection, greatly increasing the likelihood that unexpected contaminants and product variants are detected.

Summary

Intelligent automation of MS data processing using Genedata Expressionist increases throughput, boosts productivity, and ensures high-quality results that can be easily shared across organizations, making Genedata Expressionist the software of choice for MAM implementations.



❹ *New peak detection in MAM monitoring.*

The MAM Consortium
Just Biotherapeutics and Genedata are members of the MAM consortium, whose goal is to enable the BioPharma community to implement a robust mass-spectrometry-based method for biotherapeutic characterization and release of biotherapeutics from QC. Consortium members include biotherapeutic manufacturers, instrument and software vendors, and government agencies in the USA (NIST and the FDA) and Japan.

References

1. Development of a quantitative mass spectrometry multi-attribute method for characterization, quality control testing and disposition of biologics. Rogers RS, Nightlinger NS, Livingston B, Campbell P, Bailey R, Balland A. MAbs. 2015;7(5):881-90.
2. A View on the Importance of "Multi-Attribute Method" for Measuring Purity of Biopharmaceuticals and Improving Overall Control Strategy. Rogers RS, Abernathy M, Richardson DD, et al. AAPS J. 2017;20(1):7.

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