> ***Genedata developed the end-to-end oligonucleotide QC data workflow and provided the consulting expertise throughout the entire project including the validation stage to help us achieve our goals on time and within budget.***
>
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INDUSTRY
Biopharmaceuticals

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ABOUT BAYER PHARMACEUTICALS
Bayer Pharmaceuticals focuses on researching, developing, manufacturing and supplying specialty-focused innovative medicines that provide significant clinical benefit and value.

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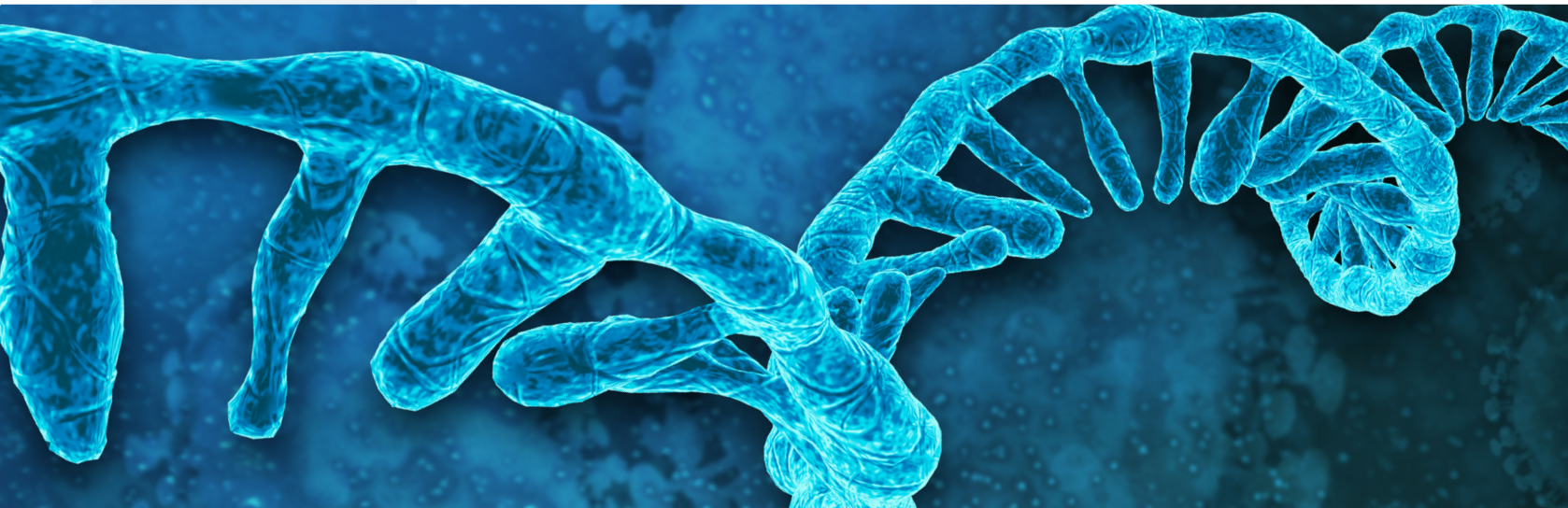
Automating QC of Therapeutic Oligonucleotides in a Regulated Manufacturing Environment

Background

Bayer Pharmaceuticals obtained an exclusive license from Ionis Pharmaceuticals to develop new oligonucleotide-based treatments for a wide range of medical conditions.

To support release testing and the imminent clinical trials of an advanced drug candidate, the Bayer Analytical Development Team for Biologics was tasked with implementing a validated drug substance and drug product release ID test that required establishing new analytical methods, standard operating procedures, and organizational responsibilities.

The tight go-live timeline and anticipated costs of any delay led Bayer to work together with our long-term partner Genedata to develop a confirmatory identification (ID) workflow of oligonucleotide species by mass spectrometry so that an approved quality control (QC) could be implemented and validated by Bayer's Quality Assurance (QA) team.



Main Challenges

Implementing an oligonucleotide analytics workflow

To ensure safety and efficacy of the new oligonucleotide drug substances, an ID test based on LC-UV-MS was translated from Ionis' standard operating procedure (SOP) into Bayer's quality management system (QMS) and implemented in a new analytical environment. This required sourcing an analytical software that allows such highly customized implementation, while also supporting the chosen instrumentation and ensuring interoperability of existing data formats. The SOP required measurement and integration of data from multiple independent analytical data streams — in this case UV and MS — to assess oligonucleotide ID (Figure 1). Automation of the workflow was critical to both reducing the overall time required to perform the analysis and providing high confidence for the ID assignment by removing any user input bias.

Satisfying GMP requirements

In order to support scheduled clinical trials, we needed to develop the ID test for the batch release of a new oligonucleotide drug product in a timely manner.
To enable the clinical deployment of the samples it was imperative that the developed analytical solution could be developed in a GMP environment. As a result, software controls were needed to ensure data security, integrity, and traceability and ultimately to confirm that every dose was safe and efficacious.

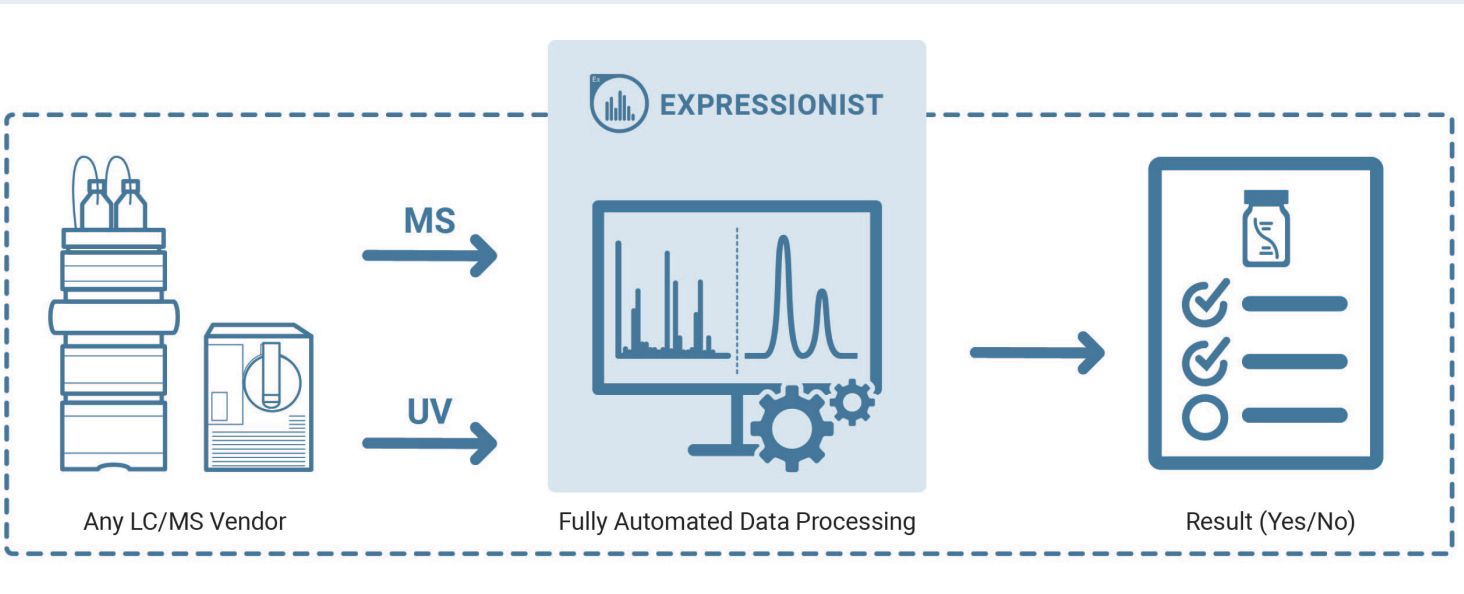
Meeting a wide range of new analytical demands

Introducing new modalities and molecular species into therapeutic development programs often requires a range of new and incremental capabilities, both technical and organizational. In this case, our aim was to establish a new QC protocol and ensure that quality assurance requirements were met.
Moreover, developing novel therapeutics poses different analytical challenges at different stages of the process. While in QC ease-of-use and robustness are key, upstream characterization and process development functions require flexibility to support in-depth molecular characterization and evolving analytical capabilities.

Solution

Swift translation of the SOP into a streamlined data processing, analysis, and reporting workflow

Genedata Expressionist enables timely implementation of highly customized MS solutions and thus the Ionis SOP could be swiftly translated into an automated end-to-end data processing, analysis, and reporting workflow.
Together with Genedata consultants, we further optimized the workflow at every processing step to meet our analytical needs and ensured compliance in Bayer's regulated downstream operations, while adhering to the SOP.



1 *Genedata Expressionist streamlines and automates complex analytical measurements, producing custom reports in any format required.*

Support for data from multiple sources

The ID test was based on analytical measurements that used MS and UV data independently and in combination. As an open and vendor-agnostic platform, Genedata Expressionist integrates seamlessly into the entire analytical process and enables us to directly import and process raw data from different instruments and combine these data streams in a single analytical measurement.

Automating oligonucleotide data analysis

The Genedata Expressionist workflow developed for this project automatically determined the first acceptance criterion (the oligonucleotide ID) by reporting the *m/z* value of the main peak. A second acceptance criterion was sample purity, which was derived from the UV data acquired in the analytical run. Although the main oligonucleotide component was visible in the UV data, impurities present in the samples were typically not observable. Extracted ion chromatograms (EICs) of the earliest and latest eluting impurity components in the MS data were used to determine the relevant areas of the UV trace to be integrated for purity measurements.

The reported sample purity result was determined automatically by the workflow. Numerous individual data calculations ensured that the areas of UV interest were correctly determined and that blank signals had been subtracted. The data integrity of the entire process — previously a highly laborious manual calculation process — was ensured by fully automating the data processing, analysis, and reporting workflow and operating it completely within the Genedata Expressionist platform.

Implementation of a System Suitability Test to provide confidence in results

Because the ID test result was subject to quality assurance requirements, a range of system suitability tests (SSTs) — such as retention time stability, relative standard deviation of peak area, reference standard purity stability, and mass accuracy — also had to be performed to ensure confidence in the ID test result.

All the SST results were determined automatically, and to simplify review, a 'traffic light' report was created to provide quick and easy identification of anomalous results (Figure 2).

Supporting deployment in a regulated GMP environment

To support deployment in regulated environments, Genedata Expressionist workflows can be 'locked down' to ensure data is processed in a manner that is not only reproducible and standardized, but also in complete accordance with the SOP. Out-of-the-box data security, integrity, and traceability allowed Bayer to implement and validate the ID test in the QC environment and meet its analytical and QA requirements while managing tight timelines. Specifically, user authentication and role management prevented unauthorized usage, electronic report submission and digital signatures ensured smooth and immutable reporting, and a full audit log provided a total overview of the chain of custody for all results.

Genedata Expressionist Features

SECURITY

User logins and administrator controls prevent unauthorized usage

Workflows can be locked down, creating an 'approved' workflow that cannot be edited by routine users

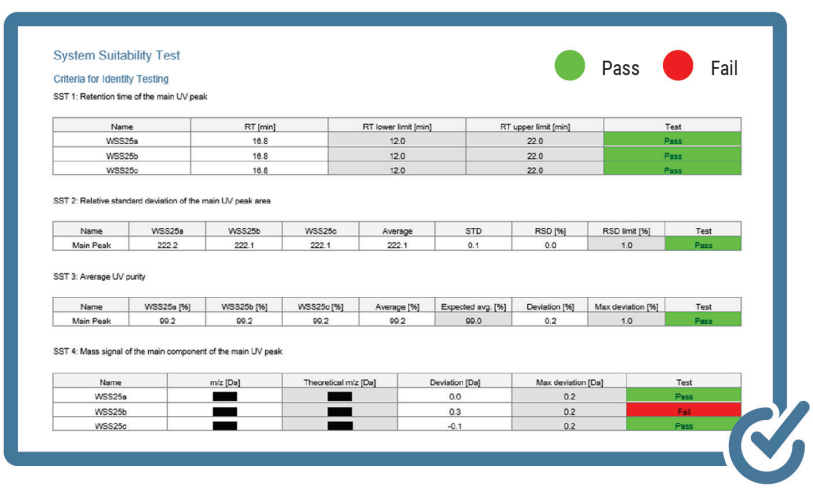
INTEGRITY

Secure and scalable client-server architecture provides confident data storage and retrieval

Report submission and digital signatures establish user controls and governance

TRACEABILITY

Audit logs give a full overview of the chain of custody and ownership of results



❷ *Compliance features of Genedata Expressionist that support deployment in regulated environments.*

Benefits

An accelerated analytical process that met all our needs

The inherent flexibility of Genedata Expressionist allied with the expertise of the Genedata scientific and technical consulting team delivered an analytical process that met all our requirements and was implemented and rolled out on time and within budget.

The ability of Genedata Expressionist to integrate multiple data streams facilitated a one-to-one translation of the existing SOP into a fully automated workflow that after training and validation could be performed by routine users. Full automation of the workflow not only ensured compliance with the SOP, but by eliminating manual process bottlenecks, also dramatically reduced data processing time by several hours.

Increased confidence and facilitated GMP deployment

Automating the workflow eliminated the risk of errors due to manual interventions and calculations, enhancing the robustness of the process and the reproducibility of results and enabling us to make decisions with the highest level of confidence. This confidence was further reinforced by 'locking down' the workflow, thereby ensuring data integrity. The transparency and stepwise nature of the Genedata Expressionist workflow enabled iterative optimization and detailed assessment of the data at every stage of processing and thereby facilitated verification of results. This, and the ability to configure and document each processing step, provided a clear demonstration of how data integrity was maintained throughout the entire process and greatly facilitated the approval of the workflow solution into Bayer's regulated environment.

Consequently, Bayer's regulatory experts could quickly assess the workflow and perform Computer Systems Validation (CSV), enabling the workflow to be established in QC within project deadlines.

Proven support for streamlining processes across the organization

Developing new classes of biopharmaceuticals — such as oligonucleotides — brings new analytical challenges. In this case, the trusted partnership between Genedata and Bayer experts enabled an effective and fast solution implementation across the entire analytical process — encompassing instrument selection and tuning; originator SOP implementation; and data processing, analysis, and reporting — in a compliant environment. The flexibility, openness, and enterprise nature of Genedata Expressionist enables Bayer to leverage the Genedata Expressionist platform on multiple levels across the entire oligonucleotide therapeutic development process, including upstream process development.

Outlook

Bayer's partnership with Genedata is built on a track-record of successful projects and Genedata Expressionist has become the platform of choice for all our MS-based biotherapeutics analytics. As we expand into the field of oligonucleotide therapeutics — and further into GxP environments — we are confident of being able to leverage the software platform to develop and implement exactly the analytical solutions we need. A key part of realizing these solutions we will be working closely together with Genedata professional services, who offer us a range of support from workflow configuration to software development.

> ***Oligonucleotide therapeutics bring new challenges, and we needed a trusted partner who could assist us in addressing them. We appreciated that Genedata offered more than just software and that the customized solution — particularly the automation — was exactly what we required.***

Dr Heiner Apeler, Department Head Analytical Development Biologics at Bayer Pharmaceuticals, Wuppertal, Germany

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