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A New Software System to Ensure Regulatory Compliance and Defensible Data

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Introduction

Regulatory bodies such as the US FDA and European Medicines Agency (EMA) are increasingly requiring more evidence of compliance to regulations such as 21 CFR Part 11[1] and Annex 11, respectively. In essence, regulated organizations must be able to both verify the identity of system users and limit system access to trained, authorized individuals. Only under these stringent conditions can data and results be used to defend biopharmaceutical submissions. While information technology and software development have enabled the automation of large amounts of work in biopharmaceutical laboratories, as Time-of-Flight (TOF)-based workflows are adopted there has been a strong need for technical controls.

We have introduced a new software system for high resolution mass spectrometry to ensure regulatory compliance in the biopharmaceutical market. The software provides workflows for biopharma characterization of intact proteins, protein digests and released glycans. In addition, recent enhancements to the MassHunter Acquisition for LC/TOF and Q-TOF, Quantitative Analysis and BioConfirm programs enable technical controls using a high-resolution LC/MS system.

Figure 1 Agilent 6545XT AdvanceBio LC/Q-TOF.

Experimental

Instrumental Analysis

LC/MS analyses were conducted on an Agilent 1290 Infinity II UHPLC system coupled with an Agilent 6545XT AdvanceBio LC/Q-TOF system equipped with an Agilent Dual Jet Stream ESI source (Figure 1). LC separation for the digested mAb sample was performed by an Agilent AdvanceBio Peptide Mapping column (2.1 X 150 mm, 2.7 µm). The instrument system was controlled by MassHunter Acquisition for LC/TOF and Q-TOF 11.0.

Data analysis was performed using Agilent MassHunter BioConfirm and Quantitative Analysis Networked Workstation 11.0 (Figures 2 and 3). The acquisition and data analysis PC was connected by secure Ethernet to an OpenLab ECM XT 2.5 server.

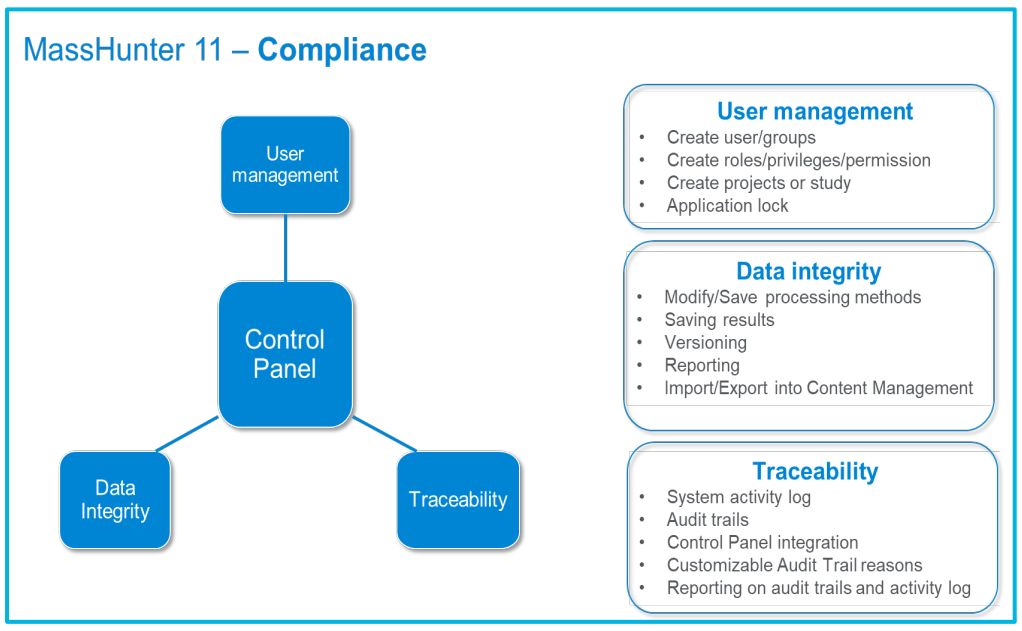

Figure 2 Overview of MassHunter 11.0 Compliance features.

	Workstation	Networked Workstation
MH Acquisition 11.0	●	●
MH Quantitation 11.0	●	●
MH BioConfirm 11.0	●	●
Software licensing	●	●
Audit trails	●	●
Access control	● (when activated)	●
Recommended for GxP labs		●
Revisions/Versioning		●
Server-based content management		●
Single point access to data from multiple sources		●

Figure 3 MassHunter 11.0 (Compliance Features) Products Comparison.

Regulatory Requirements

US FDA Part 11 in Title 21 of the Code of Federal Regulations (CFR), and its EU analog, Eudralex Chapter 4, Annex 11, describe the requirements for electronic records and electronic signatures for regulated pharmaceutical organizations. Released in 1997, 21 CFR Part 11 has been enforced since 1999. The intent of these guidelines is to ensure that all appropriate electronic records are attributable, legible, contemporaneous, original, accurate, and maintained with integrity.

21 CFR Part 11 covers three specific elements of a regulated laboratory's operation[2]:

- Security of electronic records
- Attribution of work
- Electronic signatures (if used)

Security of electronic records

To support the security requirements, OpenLab Server/ECM XT software performs automatic collection, organization, and storage of data. This occurs behind the scenes so that users do not have to do anything special to upload to this centralized single record. All data archived is versioned on the server so that older results can be reconstructed if necessary. Users can access results and reports remotely, allowing instruments and staff to continue working during data reviews and inspections.

Attribution of work

Attribution of work refers to documenting the "Who, what, when, where and why?" of work performed[3]. These can be captured in the audit trails included in the software. Figure 4 shows the new Results Audit Trail Viewer from BioConfirm 11.0. There are Audit Trails for Results, Methods, Sequences, and the dictionary of modifications that can be applied to a sequence. Audit Trail entries that have not been reviewed are highlighted in color; once they are reviewed those change to black and white. This allows a reviewer to immediately know which parts of the audit trail to review. Finally, the entire audit trail must be reviewed before it can be approved.

To support traceability, a new Control Panel allows the Administrator to set up projects, users, roles and permissions for MassHunter Acquisition for LC/TOF and Q-TOF, Quantitative Analysis and BioConfirm software.

A project is a folder that contains all the information: data files, processing methods, protein sequences and databases. Projects can have access privileges for specific users.

Users are unique in that their Username, Full Name, and Job Title are used by all the applications integrated with Control Panel. Each user cannot be duplicated nor reused.

Roles are a collection of permissions that define what assigned users can or cannot do within the software. At the time of installation, there are five predefined roles that are provided. These roles are Operator, Analyst, Scientist, Lab Manager, and Reviewer. Figure 5 shows the set up of the Scientist role and its permissions. There are no limits on the number of roles that can be created. The lab administrator can use these predefined user roles to create customized roles and assign users to them.

In addition, it is possible to set policies for an Application Lock and Timeout so a "bad actor" cannot take advantage of an authorized user's absence. Figure 6 shows the locked MassHunter BioConfirm 11.0 with its login screen.

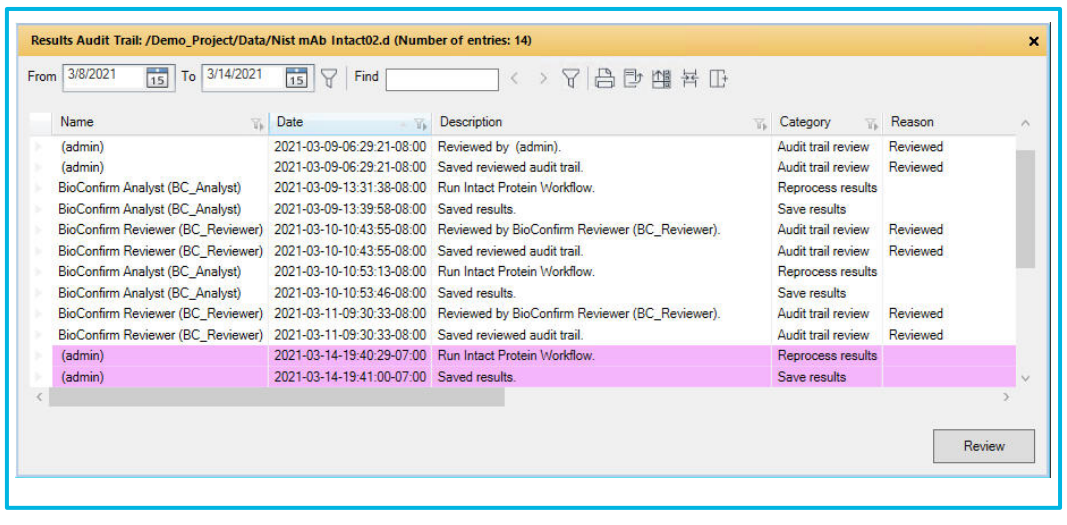

Figure 4 Results Audit Trail from BioConfirm 11.0. Audit Trail entries that have not been reviewed are highlighted in color.

Results and Discussion

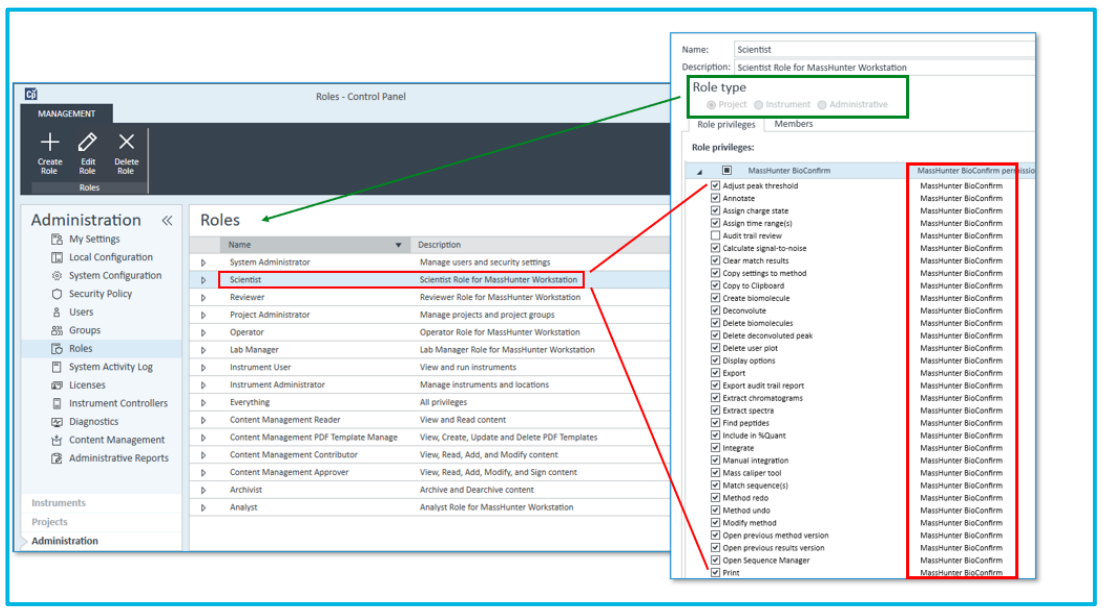

Figure 5 Control Panel with set up of the Scientist role and assigning permissions to that role.

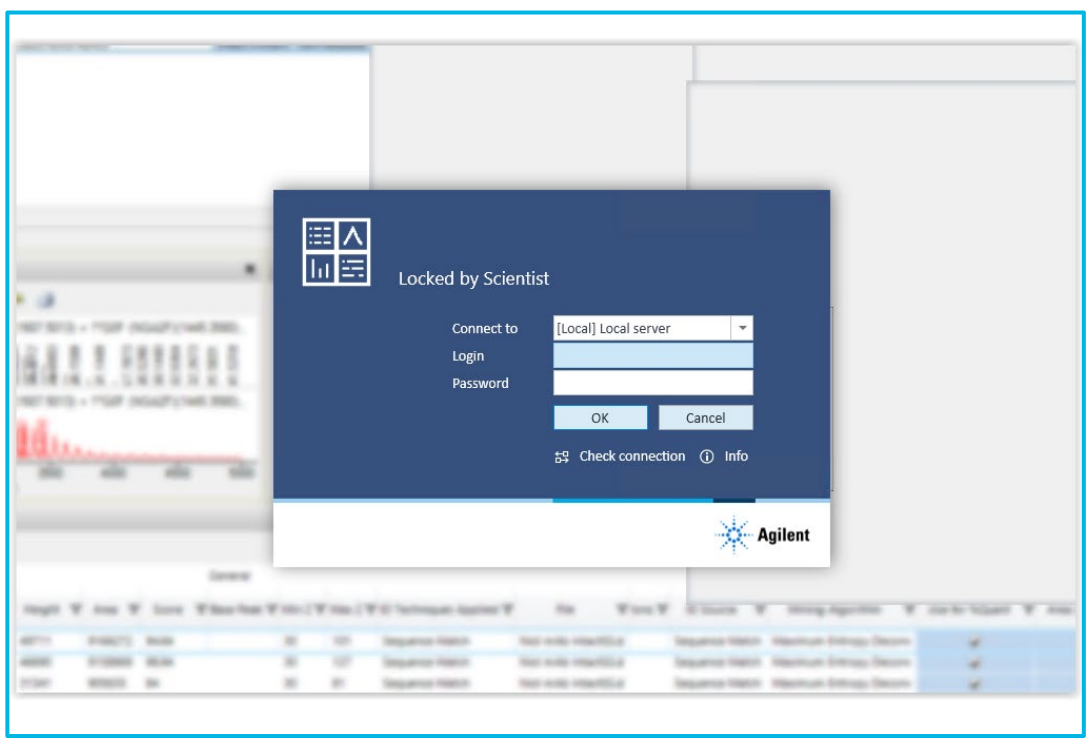

Figure 6 Locked BioConfirm with login screen and deliberately obscured software panel below it.

Electronic signatures

While 21 CFR Part 11 does not require the use of electronic signatures (eSignatures), without them a lab is committing to a hybrid paper/electronic record solution.

The software system provides a means of esigning documents. Opening the Content Browser on the OpenLab ECM XT Server allows users to access the files under content management. Browsing to a file in the project there is a checksummed fileset manifest which users with the appropriate permission can esign to approve and lock the file. Figure 7 shows the process of esigning which requires entering Username, Password and selecting a Reason, e.g. approving the document.

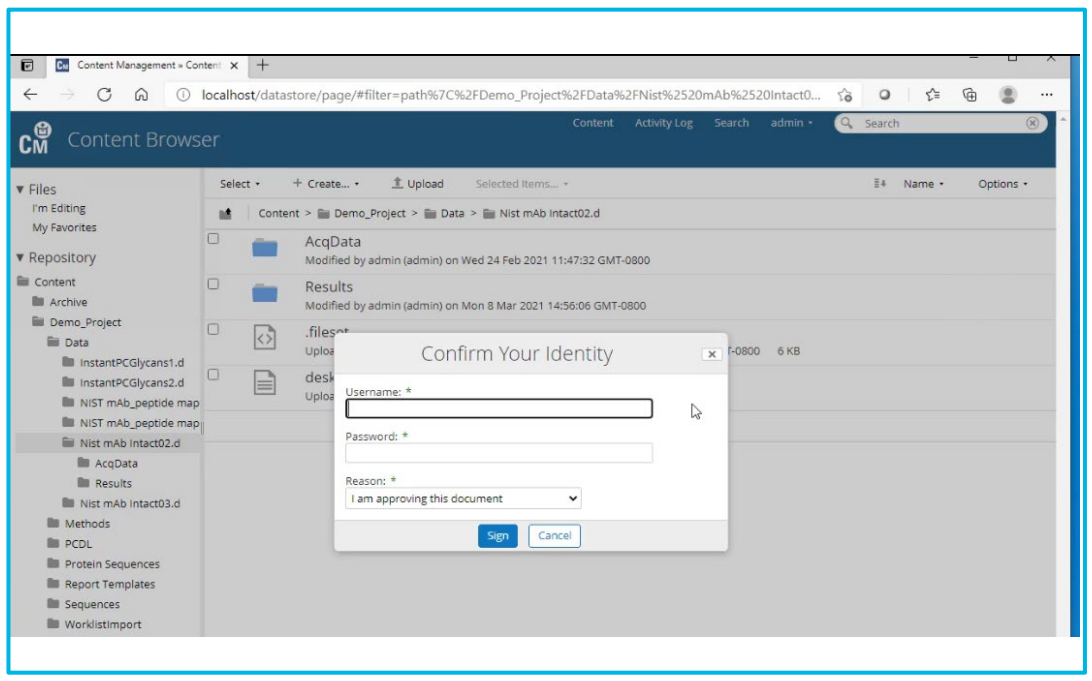

Figure 7 eSignatures require entering in a Username, Password and Reason. Only users with this permission are allowed to esign.

Conclusions

The new software system using MassHunter 11.0 enables secure and defensible data:

- Data integrity through automatic storage on a secure server with versioning and reporting
- Traceability through audit trails outlining which users did which work when
- User management through projects, defined users, roles and permissions
- eSignatures for authorized users to approve and lock documents in content management

References

[1]U.S. Food and Drug Administration. CFR - Code of Federal Regulations Title 21. Title 21—Food and Drugs, Chapter I—Food and Drug Administration Department of Health and Human Services, Subchapter A— General. Part 11 Electronic Records; Electronics Signatures.

[2]Support for Title 21 CFR Part 11and Annex 11 Compliance: Agilent MassHunter for LC/TOF andLC/Q-TOF Systems, *Agilent Technologies*, publication number 5994-2902EN.

[3]Ensuring Regulatory Compliance and Data Integrity with MassHunter Software Solutions, Agilent Technologies, publication number 5994-3546EN.

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