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Meeting Data Integrity ALCOA+ Principles Using Digital Data Management Solutions

by Sébastien Girard and Amber Watkin

Executive Summary

Proof that pharmaceutical ingredients and products have been made correctly and are safe to use is reliant on trustable data from the manufacturing process and its supply chain. The Data Integrity ALCOA+ concept defines best practice guidelines and methodologies for good data management within life science industries. This paper gives an overview of the ALCOA+ concept, its role within the digital transformation of the Life Science Industry, and offers a view on data acquisition and management solutions that help achieve the required data integrity.

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Introduction

The future of automation in life sciences is linked to Industry 4.0. The International Society for Pharmaceutical Engineering (ISPE), in collaboration with organizations such as Eurotherm®, has already developed the Pharma 4.0 concept. This will help to align the industry's digital transformation with pharmaceutical regulations and guidelines from government organizations and associations.

The 'Data Integrity by Design' approach is a key enabler for Pharma 4.0 and the ISPE has released its GAMP® RDI Good Practice Guide on the subject. To help achieve this approach, advisory and regulatory bodies have agreed on the Data Integrity ALCOA+ concept. At the time of writing, (November 2020) the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and ISPE have already released data integrity guidance documents and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) has published a draft version. The World Health Organization (WHO) has also submitted a second draft for comments, which is circulating among individual experts and organizations for review. As a long-standing internationally experienced automation supplier, well-established in life science processes, Eurotherm is an integral part of that revision process.

The WHO has a universal influence; therefore, many countries are anticipated to align themselves with their guidance. Up until now, manufacturers in some regions have avoided considering data integrity guidance. Partly, because it was not included in their local industry regulations and they were not exporting to the USA or Europe. But also, because CapEx investment was needed and the cost of training their workforce would have a major impact on their profitability and competitiveness. As the WHO guidance will aim to standardize manufacturers globally, Data Integrity ALCOA+ compliance will become a greater necessity. Building confidence in the pharmaceutical manufacturing process through trustable data records no matter which region the products are manufactured in, will enhance consumer confidence and benefit patients receiving healthcare worldwide.

To help meet the requirements of the ALCOA+ principles, the guidance is steering manufacturers away from handwritten paper-based records, towards digital recording methods. With many digital data acquisition solutions available on the market, it is important to select technology that is designed to aid data management in pharmaceutical applications, and ready to connect into Pharma 4.0 applications. Choosing an experienced equipment supplier can also provide knowledgeable engineering support and service teams to help maintain compliance in 24/7 manufacturing operations, throughout the data lifecycle.

With over 55 years' experience in providing control, automation, and data management solutions to pharmaceutical manufacturing customers, Eurotherm is considered a trusted advisor by this industry, and well placed to offer expertise and advice on data management related topics. So, what are the Data Integrity ALCOA+ principles in more detail, what issues are they trying to solve and what solutions are available?

What is ALCOA?

The acronym ‘ALCOA’ defines that data should be Attributable, Legible, Contemporaneous, Original, and Accurate. In addition to ALCOA, guidance has gone further with ALCOA+ (ALCOA plus) to recommend that data is also Complete, Consistent, Enduring, and Available. With many data acquisition options on the market, it is important to recognize the business risks related to a lack of data integrity, and poorly designed data management systems. Appreciating why ALCOA+ has been introduced and understanding the requirements will help purchasing decision makers to select a supplier with the right expertise, that can help ensure that their investment is effective and delivers an efficient solution matching their individual needs.

Attributable

- Data should be linked to its source. Thus, attributable to the individual or the system that observed and recorded it, as well as traceable to the source of the data itself.
- Changes made to data must be signed and dated by the individual making the changes

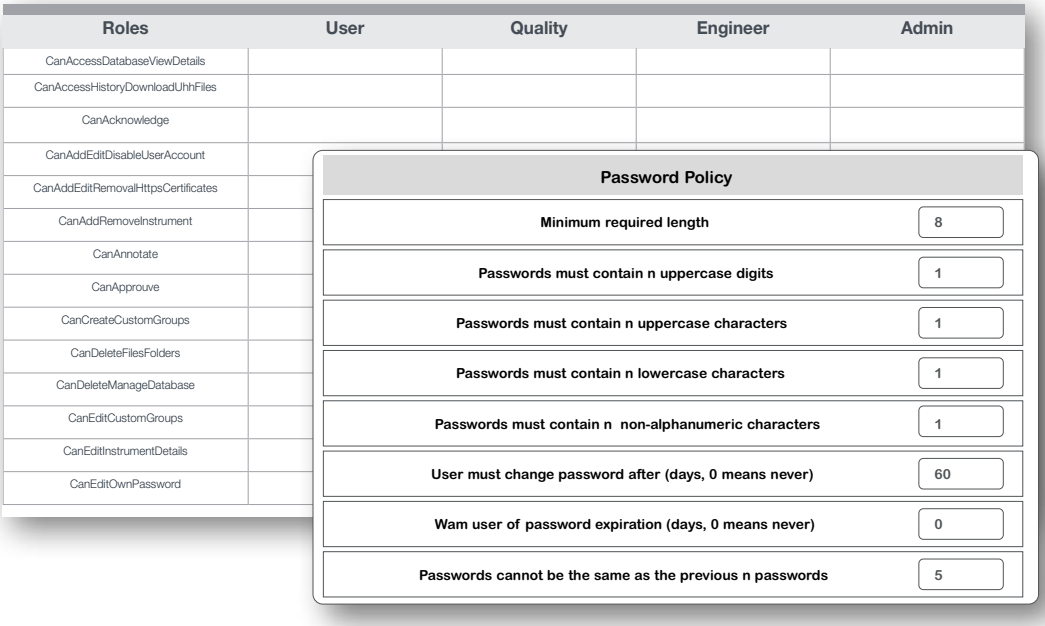
An example of bad practice is operators sharing passwords, typically due to licensing costs or slow response from IT departments to create user accounts. If individuals are able to make untraceable changes, the integrity of the data cannot be trusted. This concept of attribution applies not only to the collection of the original data but also to any changes made to it during analytics and reporting.

Data acquisition solutions can vary from a single digital data recorder to a plantwide engineered data management system. When choosing a solution, look for products and systems that have user management and audit trail features, which allow users to have individual password-protected accounts and can determine permission for which actions they can carry out by role definition. As part of the audit trail, data input changes to control parameters, setpoints, alarm acknowledgments, etc. should be automatically logged against a timestamp. A security manager feature that can be linked to Microsoft® Active Directory for simplified and centralized user management is also a worthwhile investment.

Figure 1

Example of user access and password management available for Eurotherm data recording solutions, using Eurotherm Data Reviewer Software.

- *User access permissions can be set by predefined roles*
- *An Auditor option provides extra flexibility for creating multiple roles and unique sets of permissions*
- *Password policies can be managed by the system administrator or by Microsoft Active Directory*



Legible

- Collected data must be a clear and permanent record that can be read or interpreted at any time during the retention period.

Examples of unclear records are bad handwriting, fading thermal printer paper, unsuitable scaling of data ranges, and complex audit trails. If data cannot be read correctly, risks are introduced when reviewing data for quality analysis and auditing purposes.

Moving from paper-based recorders and manual paper reporting, to digital graphic recorders and reporting software, helps to reduce the need for handwritten records. The digitally recorded data can then be stored, retrieved, and printed, providing a readable audit trail for periodic review. Typically, the recorded data files can be archived and reviewed using a software package. For ease of use, look for software that can automatically search for data by the recording device name, group, batch code, or date range for quick retrieval.

Some packages have Auditor options available, which allow comments to be added, as well as approval or validation using electronic signatures at any point during analysis. It is important that these notes are subsequently stored alongside the original data for easy retrieval later. Selecting software that can automatically print defined charts, channel values, messages, and alarms upon batch completion is also beneficial for quality personnel. Data can be archived in a historian server to provide data for analysis and report creation. Digital reporting packages are available for creating easily readable reports from simple pass/fail to sophisticated analytics, created either manually, or automatically from defined templates.

Figure 2

Example views of chart record, annotation and PDF reports available for Eurotherm data recording solutions, using Eurotherm Data Reviewer Software.

- *Historical review of digital data trends and operator messages*
- *Add comments digitally for review, approval and release*
- *Create, view and store required chart data and comments in easy to read PDF format*

Contemporaneous

- Data must be recorded at the time it was generated or as close to the observed event as possible.

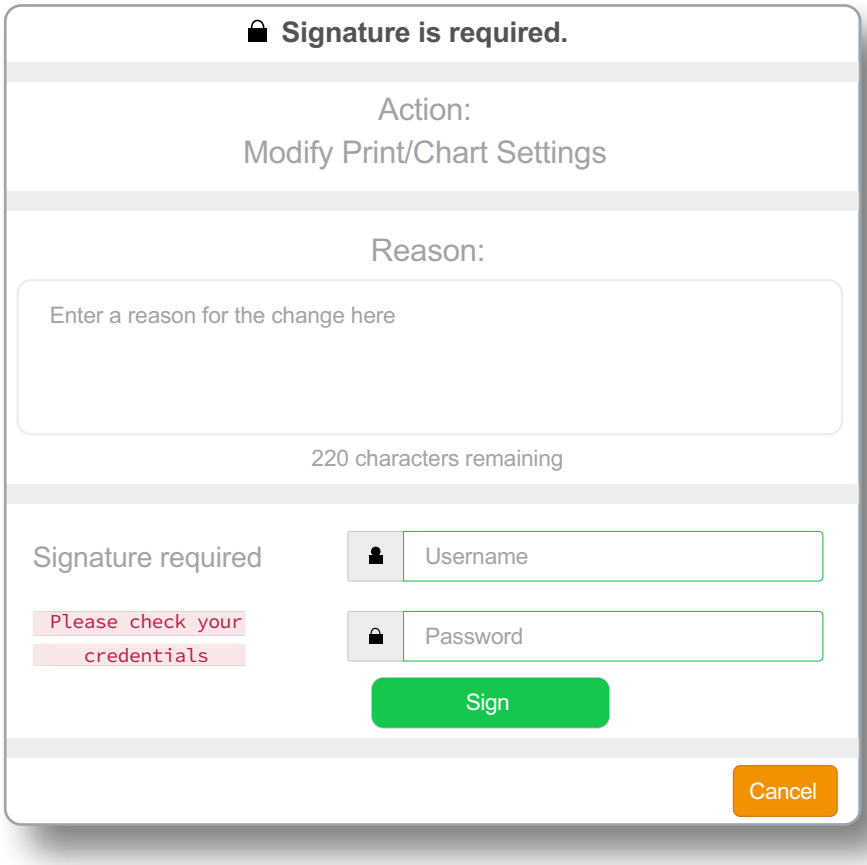
Back-dating of data can result in mistakes, and information can be forgotten if written at the end of the operation or day. Another example of bad practice is the re-use of previous good batch results or the re-testing of borderline results, which can misrepresent the true pass/fail status. Therefore, the data integrity requirements ask for timestamping without manual operation, with the recording device and computer time clocks synchronized across the system. Typically, this is achieved via an SNTP (Simple Network Time Protocol) server.

Again, using capable digital recording products allows comments associated with alarm acknowledgment or signed parameter changes to be entered and recorded at the time of the action. It should be possible for process and alarm data to be gathered automatically via predetermined, validated functions with no manual intervention. Alarm acknowledgment comments and parameter change signatures should be automatically entered against the relevant timestamp. For automatic time synchronization, choose devices that can be connected over a network to an SNTP server. Some data recorders are available with SNTP server functionality built in, for synchronizing their connected devices.

Figure 3

Example of electronic signature available within Eurotherm Data Reviewer Software with Auditor option.

- *Auditor option provides support for electronic signatures in accordance with FDA 21 CFR Part 11 and Data Integrity ALCOA+ requirements*
- *Data Reviewer Enterprise edition includes an Audit Trail*
- *Changes are timestamped and stored with the process data*



Original

- Original data, termed as ‘source’ or ‘raw’ data is generally considered to be the first and therefore the most accurate and reliable record.
- Whether resulting in a pass or fail, this data should be preserved in its original unaltered state or recorded as a true certified copy for reference.
- Any calculations, reports, and analysis results are considered as ‘metadata’ in reference to the raw data.
- During audits, auditors will expect to be able to trace metadata, like reports, directly back to the source/raw data.

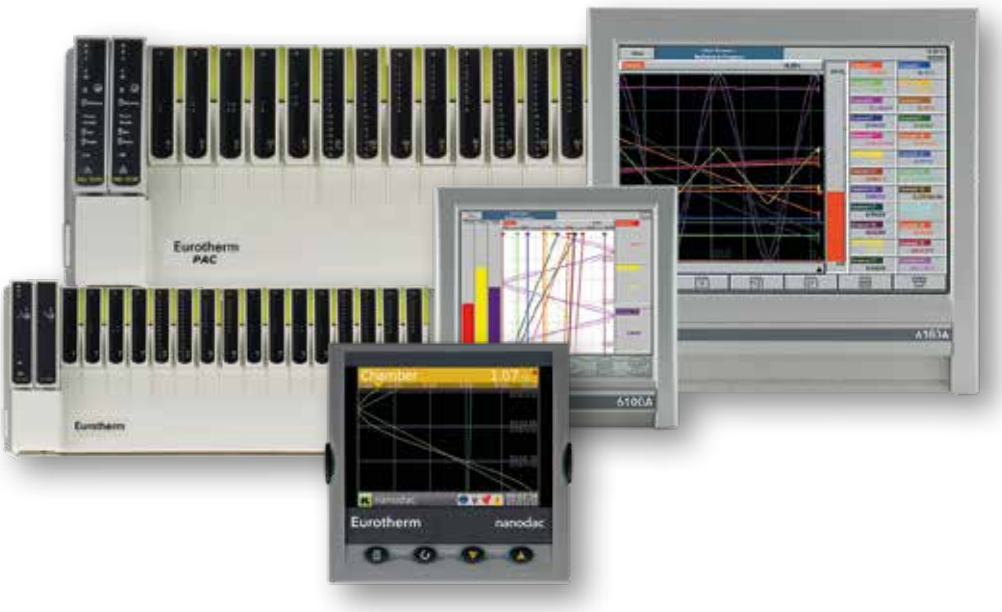
Using paper-based records can cause issues, as data can easily be modified and misinterpreted. Re-writing of data can result in incorrect data entry, and unsuitable rounding of numeric values can lead to misleading results. Digitally recording data in the commonly used .CSV file format should also not be relied upon to represent original data, due to its easily editable plain text format.

To help life science companies prove the validity of their original data, some equipment suppliers have developed tamper resistant data file formats. For example, in Eurotherm data recorders, process data and alarm messages are stored in a binary-checksummed proprietary .UHH file format. Trends and reports can be read from this file type using the proprietary Data Reviewer software tool, which uses predetermined functions and can be validated as creating a true copy. It is also able to discern and reject altered records.

Figure 4

Eurotherm data acquisition products record data in a proprietary tamper resistant file format, readable using Data Reviewer Software.

- *Example shows: 2750 PAC controller versadac™ scalable recorder*
- *6180 and 6100 graphical data recorders*
- *nanodac™ recorder controller*



Accurate

- The data records should correctly reflect the action or observation made and data should be checked where necessary.
- Any modifications must be explained if not self-evident.

Accuracy is an implied element of data quality across good practice (GxP) guidelines. Advice now encourages the use of electronic data capture instead of paper, and to build accuracy checks into the design of the electronic system. Care needs to be taken when selecting recording solutions to ensure the recording device has suitable accuracy specifications. Sensors also need to be placed in suitable positions, otherwise, readings can be interpreted incorrectly. Equipment accuracy measurements can drift over time, so calibration needs to be carried out at specified intervals.

An electronic format can offer clearer data accuracy and higher resolution compared to paper records. Look for data acquisition products with high accuracy input specifications designed to provide precise measurement in electrically noisy manufacturing environments. Digital recorders typically have easy range parameter settings for entering suitable data limits. Built-in procedures to cover instrument loop calibration are often a necessary feature, to confirm that values read are representative of the actual process conditions.

To relieve the burden of calibration, some solution providers offer comprehensive calibration services. Those specializing in life science applications also offer qualification and validation services to help meet ISPE GAMP® 5 guidelines. The management of process equipment calibration and other equipment tests can be optimized plantwide by using a cloud-hosted digital service platform.

What is ALCOA+?

The plus (+) part defines four additional data integrity requirements, that apply to the basic ALCOA principles.

Complete

- All relevant raw data and metadata must be collected, including retests or reanalysis.

To help capture complete data, choose solutions that can store information such as process values, batch details, alarm history, and audit trails, all together in the same data file. Features designed for auditing activities should be able to capture information such as alarm changes and acknowledgment comments for review.

Consistent

- For consistency, all elements of the analysis should be date/time stamped and in the expected sequence, including deviations that occurred during the process, and any changes made to data.

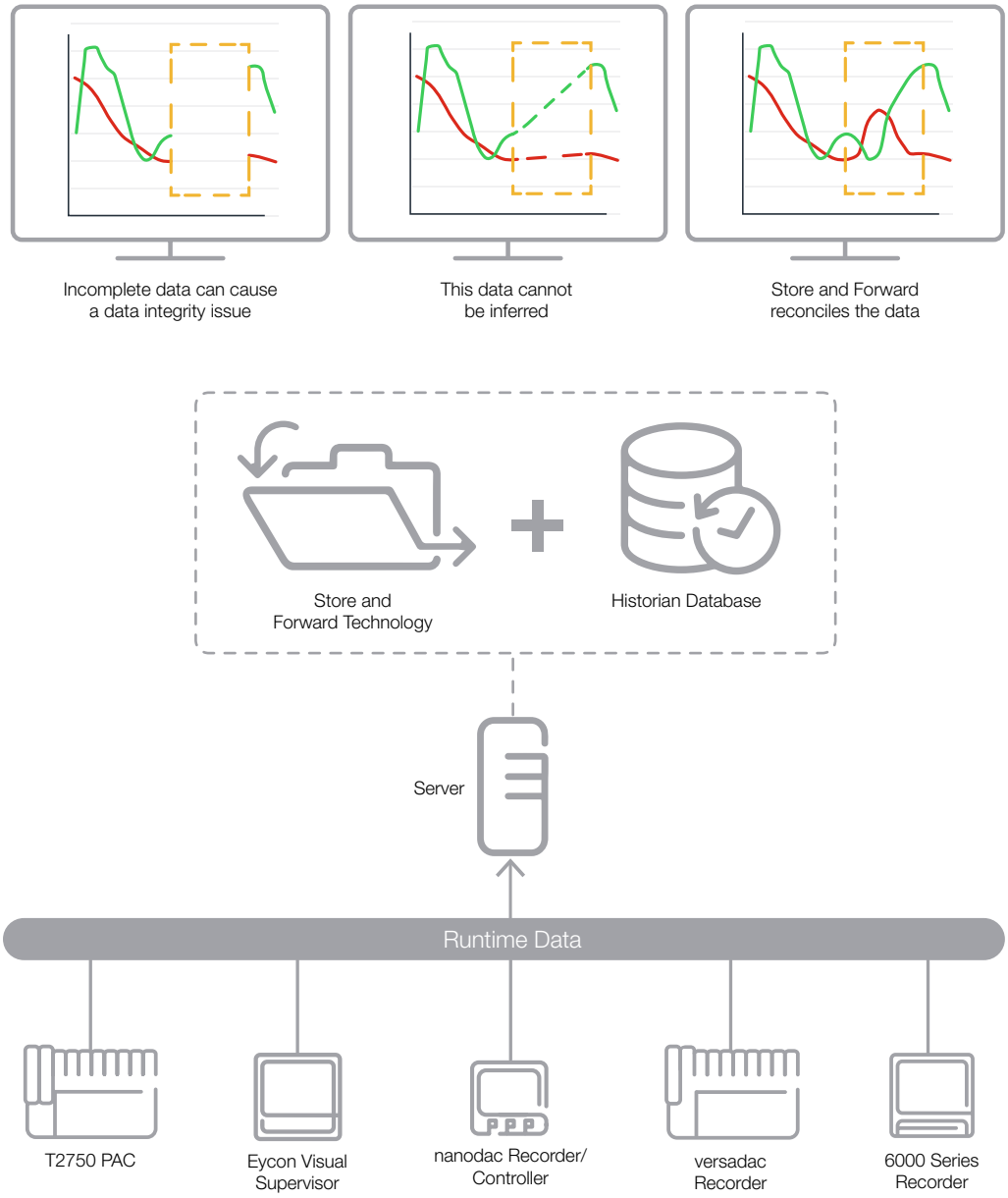
Using a digital data recorder that can make use of network time synchronization and has built-in memory devices enables the recording of data at the right time at the point of measurement. Storing the data initially in the recorder device reduces the risk of data loss if communications are temporarily lost.

Features that store and forward the data can aid reliability of archiving, by backfilling data to storage databases when communications are resumed. Again, data must be stored in a timestamped format to aid data consistency.

Figure 5

Eurotherm data acquisition products record data at the point of measurement for archiving later, reducing the risk of data loss if the server or communications are temporarily lost.

- *When used in harmony with a historian server, the Eurotherm 'Store and Forward' feature aids reliability of archiving, by reconciling any missing data to storage databases when communications are resumed*
- *This supports the Data Integrity ALCOA+ concept by providing original, attributable data that is contemporaneous, consistent, and complete*



Enduring

- Data records should be stored as controlled documents or electronic media for longevity

High availability system architectures, including uninterruptable power supplies (UPS), and redundant instrumentation, servers, historians, and communication networks can be implemented to support long term data retention for continuous compliance in regulated applications. It is advisable to put automated data backup and disaster recovery plans in place, which can also be carried out as a service by capable suppliers.

Available

- Data must be available and readable by the responsible personnel for retention period.

Tamper resistant electronic file formats and the use of high integrity data historians enable long term storage and availability of the data throughout the life of the record, generally a specified time after the product expiry date. Again, implementing data backup and recovery plans will also help.

The data lifecycle

Data Integrity ALCOA+ principles apply through all phases in the life of the data, from initial generation and recording through processing, use, data retention, archiving, and retrieval up to its destruction date.

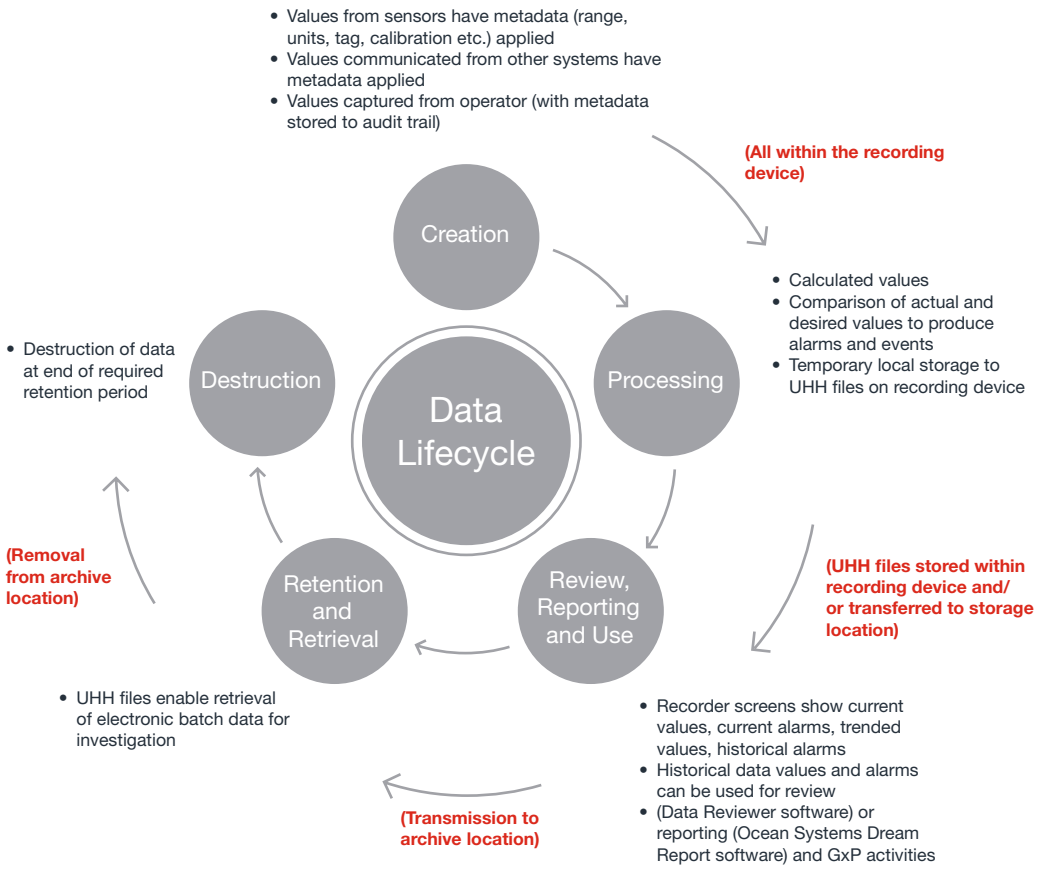


Figure 6

An example of how Eurotherm data acquisition solutions aid compliance with ALCOA+ and FDA 21 CFR part 11 data integrity requirements throughout the data lifecycle.

Pharma 4.0 ready technology

The ISPE and automation suppliers such as Eurotherm have introduced Industry 4.0 to the pharmaceutical industry as ‘Pharma 4.0’, providing best practice guidance and a holistic approach for the industry’s digital transformation. Its ‘data integrity by design’ approach is a key enabler for Pharma 4.0, aiming to fully embed data integrity into automated manufacturing environments as standard practice. The guidance states that data collection processes and data flows need to be well defined and documented throughout the systems involved in the manufacturing process, following the ALCOA+ principles. Achieving this will require the transformation to paperless execution systems utilizing digital technologies.

Eurotherm control and data recording solutions are IoT ready, providing a data integrity layer within open IoT platform system architectures and aiding the digital transformation to Industry 4.0 technology.

Plant Performance Advisors, AVEVA Historian and Eurotherm Data Reviewer are a few examples of software packages that can help pharmaceutical manufacturers to turn the volumes of data they produce into actionable insights, enabling the modernization and scaling up of production.

- Plant Performance Advisors Suite for Smart Operations is a specialized suite of smart manufacturing apps and digital services, providing data-driven manufacturers with easy to understand real time analytics for prompt decision-making.
- AVEVA Historian provides high-speed data collection using specialized data storage algorithms that greatly reduce data storage requirements while helping to preserve data integrity in its embedded database. Low bandwidth data communications, and data from systems with mismatched system clocks can be managed, aiding compliance to Data Integrity ALCOA+ principles.
- Eurotherm Data Reviewer is a software application designed for viewing, analyzing, and printing historical data files obtained from Eurotherm data acquisition equipment. The Enterprise version is a server-based software with unrestricted database size and multi user access, offering role-based access to data over corporate networks for quality audit and reporting purposes.

Cybersecurity

When utilizing digital data acquisition products in pharmaceutical research or manufacturing environments, it is important to consider cybersecurity as part of the overall data integrity strategy. Business-critical data such as process values, recipes and intellectual property (IP) need to be protected, as well as business-critical operations. The installation's design should therefore aim to prevent unauthorized and malicious access. This includes both physical access (for instance, via the product front panel or USB connections), and electronic access (via network connections and digital communications).

A business risk-based approach can often help to achieve a practical balance of threat mitigation compared to cost. Following the guidance in defined standards such as ISA/IEC 62443 can help to instill the necessary processes and procedures into a business and its project work to deliver a desired level of security, both when a system is installed, and then into its operational phase.

Typically, to reduce the chance of unauthorized access to process control and operations level devices, the identified risk mitigation will dictate that they should not be placed on a network with direct access to the public Internet. Instead, good practice involves locating the devices within a fire-walled network segment, separated from the public Internet and local business network by a so-called 'demilitarized zone' (DMZ). Best practice considers that relevant communication channels and ports should be disabled by default and only enabled if required.

For more information on cybersecurity see Eurotherm Cybersecurity Good Practices Guide

Should a malicious attack penetrate defenses, targeted robustness of the control and operations devices can limit the impact. For example, control and data acquisition products are available with features such as 'rate protection' and 'broadcast protection' algorithms. These algorithms can detect excessive network activity and help to ensure that a device's resources are prioritized on the control/recording strategy, rather than servicing the network traffic.
As a guide, look for products certified under the Achilles® Communications Robustness Test Certification scheme. This is an established industry benchmark for the deployment of robust industrial devices, recognized by the major automation vendors and operators.

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Reliance upon a single means of security would not normally offer optimal risk mitigation. Instead, a multilayer approach based on ‘defense in depth’ would provide more protection, especially when coupled with a balanced approach driven by a risk assessment, with additional countermeasures applied to the most critical areas identified.

Figure 10

For example, the Eurotherm EPC3000 programmable controller range shown has Achilles Level 1 certification.

Other certified Eurotherm products include:

- *EPC2000 programmable controller*
- *T2750 PAC controller*
- *EPack™ power controller*

Eurotherm data recorders available with features for enhanced cybersecurity robustness include:

- *6000 series data recorders nanodac recorder controller*

A range of cybersecurity services are available from Eurotherm to help improve data integrity from an operational technology (OT) perspective in industrial control systems (ICS), and corporate network information technology (IT) systems. These include cybersecurity audits for use in business risk assessments, step by step improvement upgrades, software upgrade/patching services, and ‘disaster and recovery management’ designed to help the installation meet the ISA/IEC 62443 standard.

Choosing the right supplier

When selecting a product or system supplier, do not overlook the value provided by a knowledgeable engineering team. How well do they understand pharmaceutical manufacturing processes, control, automation and data acquisition applications, compliance to industry standards, and the importance of business key performance indicators (KPIs) and company goals? An experienced solution provider can offer extended support through engineering and services.

Consider the benefits of a company with expertise in:

- System engineering and operator interface design
- Operator and maintenance training programs
- Qualification/validation to ISPE GAMP® 5 guidelines
- Calibration and asset management
- Parametric batch release
- Warehouse mapping
- Environmental monitoring systems (EMS)
- Energy and cybersecurity surveys

Service level agreements (SLAs) are also a popular choice for life science manufacturers. Typical services can include:

- 24/7 telephone support
- On-site engineering assistance
- Remote diagnostics and application support
- Predictive and preventative maintenance
- Equipment health checks
- System upgrades
- Software updates and patch management with change control
- Disaster and recovery plans
- On/offsite spares management and repairs
- Qualification/validation with change control

While data integrity should now be embedded in a life science manufacturing process, ease of use for operators should also be considered. For example, procedural workflows and operator interfaces designed for situational awareness can help even unskilled operators to take the correct actions.

Control and data management suppliers with a long history in life sciences will have the industry knowledge, expertise, and familiarity to understand the subtleties of pharmaceutical applications combined with the know-how to design up-to-date smart manufacturing systems. Suppliers that are members of pharmaceutical organizations such as the ISPE should have a good understanding of the data integrity and change control requirements of pharmaceutical manufacturing environments and be able to act as a trusted advisor on good manufacturing practices.

For global manufacturers, a supplier with a worldwide network of project engineering teams and approved solution providers should be able to support the design and specification of system projects initiated in one country for delivery in other regions. A company that can provide global alliance agreements can help to deliver supply chain standardization and cost efficiency, as well as process consistency across international plants. Solution providers with strong partner collaboration networks are typically able to create the most effective offerings by combining superior solutions and services.

Conclusion

With the continuing introduction of Data Integrity ALCOA+ principles across the world, pharmaceutical manufacturers can no longer ignore the guidance. Understanding the data integrity requirements of the ALCOA+ principles will help life science companies to select suitable data acquisition solutions and services that simplify regulatory compliance and aid connectivity with Pharma 4.0 technologies. Choosing a solution provider with pharmaceutical application knowledge and expertise, whose products, solutions, and services are designed with data integrity features embedded, will greatly support the move to compliant digital data acquisition, recording, retention, and retrieval.

About Eurotherm

With a long history in precision process control, automation, and high integrity data management, Eurotherm has a broad range of knowledge and expertise in regulated industries, including life sciences, helping customers to comply with data integrity related standards and guidelines,
such as

- U.S. FDA 21 CFR Part 11
- EU EudraLex Annex 11
- GxP
- Data Integrityn ALCOA+

As well as providing a range of control and data acquisition products and engineered systems, Eurotherm provides a wealth of expertise in life science applications, offering comprehensive engineering support and services, such as calibration, qualification/validation aligned with ISPE GAMP 5 guidelines, data management, energy management, and cybersecurity services. For more information on solutions that help meet ALCOA+ data integrity guidelines, visit:

www.eurotherm.com/data-integrity-ls

About the authors

Sébastien Girard has over 30 years' experience in providing Eurotherm solutions for Life Science applications covering R&D lab to pilot plant to full-scale production. Sébastien is a member of the ISPE and A3P associations and is a regular contributor at global seminars and conferences, offering advice and expertise on data integrity subjects.

Amber Watkin has over 25 years' experience in the Eurotherm portfolio, across Glass, Heat Treatment, Semiconductor, Life Science, and Food and Beverage industries. She is knowledgeable about Eurotherm energy saving, efficiency enhancing solutions and services, designed for energy intensive, high performance, specialized and regulated thermal processing applications.

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