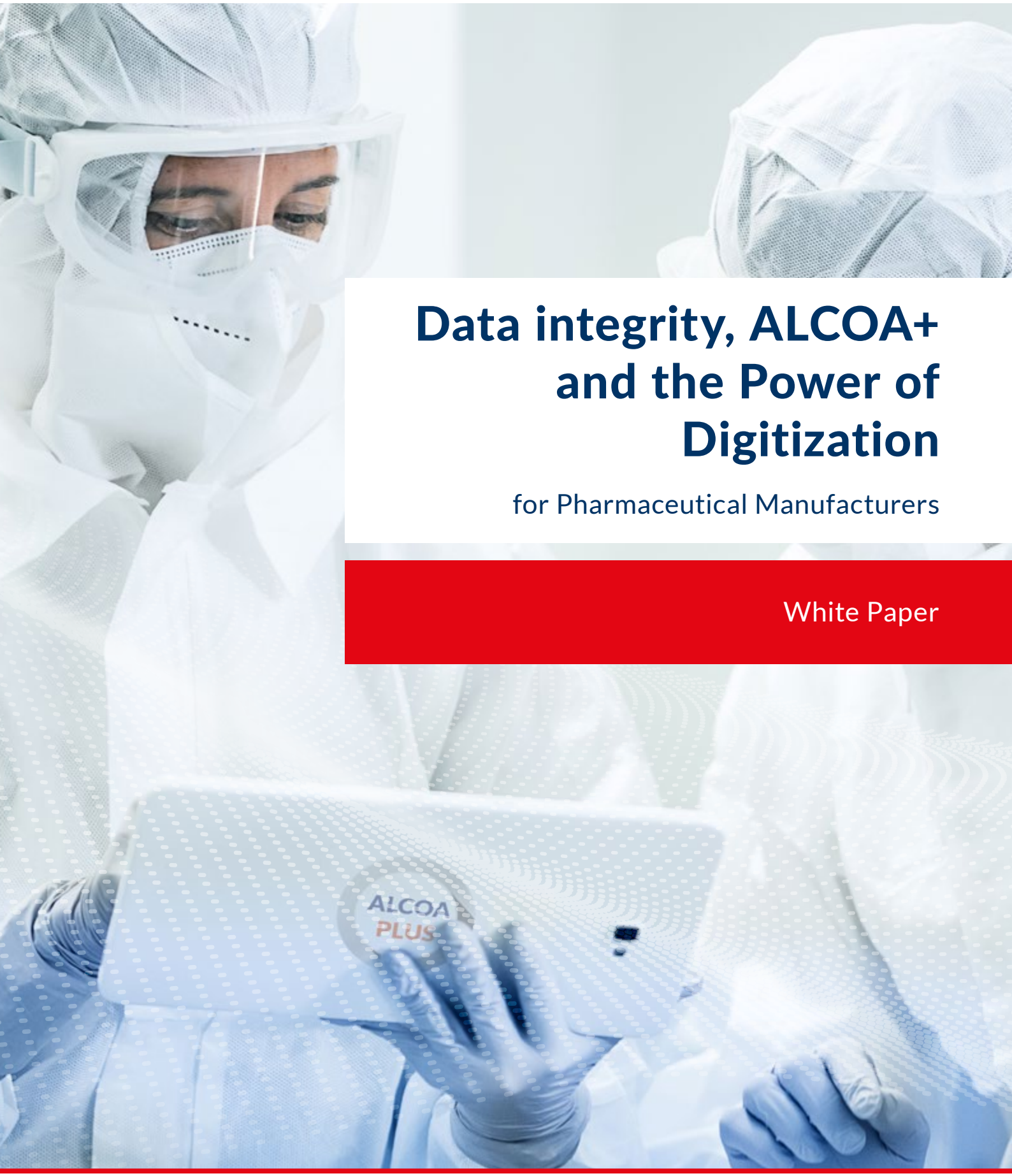
PST
PROCESS SENSING
TECHNOLOGIES



Data integrity, ALCOA+ and the Power of Digitization

for Pharmaceutical Manufacturers

White Paper

MICHELL Instruments · Analytical Industries Inc · rotronic MEASUREMENT SOLUTIONS · LDetek · DYNAMENT INFRARED GAS SENSORS · NTRON Gas Measurement · SST

Content

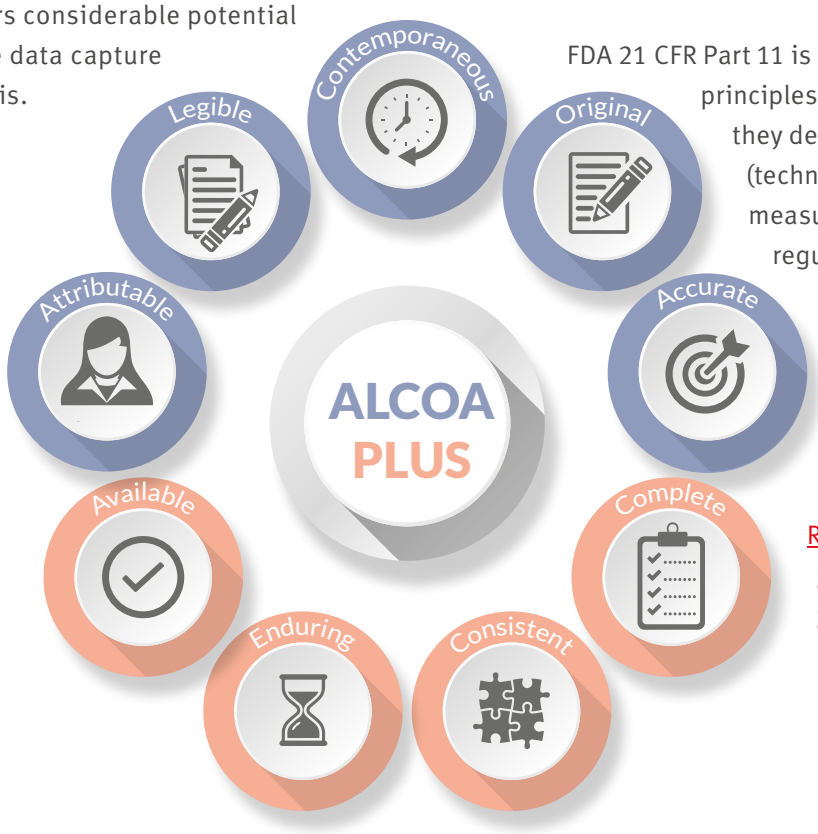
The need for data integrity

Data – the critical information required for the operation, maintenance and management of pharmaceutical production processes – has always been important. Today, new technologies, the growth of automation and integrated Pharma 4.0 systems, globalization of supply chains and ever-tougher international regulation are changing the role of data into a mission-critical requirement for the safe, compliant and profitable function of pharmaceutical manufacturing.

One of the strengths of modern digital technology – its ability to generate large and varied volumes of data in real time – can also become a potential liability if the data generated threatens to overwhelm the ability of existing systems to process, analyze and react to different inputs and emerging trends, or if the data is siloed or otherwise disconnected.

In essence, data has intrinsic value, but is of no use unless its integrity can be verified and actionable valuable insights derived from it.

This is where ALCOA and its update ALCOA+ have a vital role to play for pharmaceutical producers, and where the Rotronic Realtime Monitoring System (RMS) offers considerable potential in effective data capture and analysis.



ALCOA & ALCOA+

Data integrity is essential for both regulatory compliance and production efficiency. ALCOA was originally introduced as a data integrity mechanism to define best practice guidelines and methodologies for good management practice within the pharmaceutical and life sciences sectors.

The original definition of ALCOA was implemented by the US Food and Drug Administration (FDA) in the early nineteen nineties. This set out a series of five principles under the headings of: Attributable, Legible, Contemporaneous, Original and Accurate. Some years later, these were extended under ALCOA+ to include: Complete, Consistent, Enduring and Available.

These principles have subsequently been adopted by many international and national regulatory and advisory bodies, including the World Health Organization (WHO), European Medicines Agency (EMA) and the International Society for Pharmaceutical Engineering (ISPE). Today, the principles of ALCOA+ apply to both paper and electronic records and provide a framework for handling data as part of Good Manufacturing Practices (GMP) and Good Documentation Practices (GDP), within for example the FDA regulation 21 CFR Part 11.

FDA 21 CFR Part 11 is a good example of how the ALCOA principles have been adopted. For example, they define the software functionality (technical solution) and administrative measures (procedural control) that a regulated user should put in place for compliant system operation. This approach forms the basis for our RMS solution, covering its methodology and compliance. These are explained in detail in our separate white paper: Rotronic RMS System eCompliance. If you would like a copy please contact your Rotronic representative.

What do the ALCOA definitions mean?

The ALCOA and ALCOA+ definitions have been carefully constructed and tested by different industry bodies and are generally interpreted as explained below.

Attributable

The first principle of ALCOA is that all data must be attributable or linked to a specific source. This is typically the person or automated system that monitored or recorded the data, as well as the device from which the data was captured. Similarly, any subsequent changes to the data must also be signed and dated by the person making the changes.

This is an important first principle of traceability and requires that best practice guidelines be rigorously followed. For example, it can often be convenient for different production line staff to share access passwords to system devices; this does, however, mean that changes to operating parameters can be difficult to trace.

Although data acquisition devices can range from simple sensors and digital data recorders to plant-wide data management systems, it is important to ensure that each device offers the functionality to allow dedicated user-access management. Typically, this will include individual password-protected accounts and role-based user-permissions, with an automated audit trail. It is therefore easy to identify the source and timing of any changes to operating parameters, such as setpoints and alarms, and to attribute these changes to particular individuals.

The RMS solution

The Rotronic Realtime Monitoring System is designed to ensure that the entire system is attributable. Each user-created element is given a unique denomination, which is automatically defined and cannot subsequently be modified, to provide full accountability and traceability.

The associated audit trail uses the output from digital data loggers to ensure that, for example, all product replacements (for repair or calibration purposes) are automatically documented.

Similarly, individual password protected accounts and role-based user permissions mean that every change within the system can easily be traced back to the user responsible for the change, with the process values before and after the change, as well as the reason for the change, being captured in accordance with FDA 21 CFR 11 requirements.

Legible

In some respects, this principle refers back to the time when hand-written and paper based records were widely used. Nonetheless, the principle of legibility remains valid in today's, largely digitized production environment, as print-outs together with any manually added annotations must be easy to read and archivable to provide a clear and permanent record of all activities and changes. It is also worth noting that hand-written records should not contain unusual acronyms or notes that may be difficult to understand in the future if the originator of the information has moved on.

Moving from paper-based to digital records eliminates many of these potential issues. The key is to use a system that allows easy recording, storage and retrieval of data, ideally with an intuitive user interface and software that can automatically locate data using, for example, the recording device name, group, batch code or date range as search criteria. Additionally, software should be able to collate and output reports for use by quality, production or maintenance teams.

The RMS solution

The Rotronic Realtime Monitoring System builds on the principle of individual password protected user accounts by using defined signatures, which can be set for each individual user.

Additionally, signatures based on specific actions as defined within the FDA 21 CFR Part 11 regulations can be set. All events are automatically created within the audit trail, with users with appropriate permissions being able to comment or approve actions or changes in process conditions.

This ensures legibility and accountability, while providing a secure record for subsequent quality assurance purposes. All inputs are always visible within the audit trail.

Contemporaneous

One of the key aspects of verified data collection and analysis is that it is captured as close as possible to the time that each event occurs. This is perhaps of greater relevance to manual data collection, where it is common for data recording to be back-dated; clearly this creates a potential risk that information goes unreported, is incorrectly remembered or, in a worst-case scenario, deliberately misrepresented.

This ceases to be an issue with automatic data collection, where each event is recorded as it occurs and is time-stamped accordingly. This does, however, depend on having a system that avoids queuing data processing, with correctly configured system clocks and time-zones. This is normally achieved using a networked SNTP (Simple Network Time Protocol) server or devices with SNTP functionality built-in.

The RMS solution

The Realtime Monitoring System software application makes full use of standardized SNTP functionality. All RMS devices continuously synchronize with the RMS application, ensuring that device real-time clocks are always up to date and events captured in real-time.

To extend this benefit still further, RMS hardware can be either wired or wireless, with multiple, user-selectable measurement intervals, from 10 seconds to 15 minutes.

The overall system is designed to allow users easily to customize each process; for example, process managers can decide which critical control parameters need to be monitored and the level of on-demand data access.

Original

For both paper-based and digital systems, the preferred option is to capture and retain the original data record in its unaltered state; this is sometimes referred to as source or raw data.

Although it is clearly easier for operators to copy and duplicate paper records, for example to rewrite or update data entries, and thus risk losing the source data, it should not be assumed that digital records will automatically be immune from modification. This is especially true if data is captured using the common and easily edited plain text .csv format.

In each case, the key is to have robust technical and procedural processes in place to validate and protect the integrity of source data. With digital systems this can often be achieved by using devices that are password protected against unauthorized data manipulation, or which use proprietary file formats that can only be interpreted by appropriate reporting software.

The RMS solution

Once RMS devices are setup within the RMS application they are automatically protected against unauthorized data manipulation. All data collected is stored on a protected server. If changes are made to the raw data, they will automatically be recognized and reported by the RMS application.

All PDF documents created within RMS, such as calibration reports, qualification reports, validation reports and electronic production records, with the user's name and signature, can easily be checked for authenticity via the RMS platform.

Accurate

Accuracy is a key prerequisite of ALCOA, ALCOA+ and, indeed, all good practice (GxP) methodologies. This is not always easy to ensure with paper based systems, which can be prone to human error. Consequently, best practice is to now to use electronic methods of data capture. This does, of course, depend on equipment being correctly specified, setup, operated and maintained.

Data acquisition instruments should be selected for their levels of accuracy, reliability and repeatability, as well as ease of use and ability to be integrated within process-wide monitoring and control networks. Although cost will always be a factor in the choice of any production equipment, in this instance cost should be a minor consideration as these instruments are essentially mission-critical and any failure or inaccuracy could have potentially far-reaching effects.

It is also important to carry out regular instrument recalibration to eliminate problems of, for example, sensor drift. Many suppliers, including Process Sensing Technologies, offer calibration as part of their aftersales services.

The RMS solution

Rotronic offers the most accurate, reliable and repeatable measurement devices on the market. These devices are calibrated either directly or traceable to the ISO17025 calibration standards, with reliability and repeatability being verifiable through the calibration history of each device. Within an RMS system, devices such as measurement probes communicate digitally with data loggers, preventing the degradation of data. They are also quick and simple to replace when recalibration is required, with our support services including the supply of fully calibrated and certified swap-out probes. Any change to the measurement devices is automatically recorded in the RMS audit trail.

We also offer the HG2 temperature and relative humidity generator for on-site calibration of temperature and humidity probes, while our chilled mirror hygrometer can be used as reference instruments. Our ISO17025 accredited calibration laboratories offer a fast and efficient range of services and we offer detailed calibration seminars.

ALCOA+

The success with which the original ALCOA principles were adopted by the pharmaceutical sector, together with the more recent need to refine and extend the operating model, has subsequently led to the introduction of ALCOA+. This builds on the original definitions by adding the following categories:

Complete

There should be a complete record of all activities to enable an accurate and fully detailed audit trail to be constructed.Thus, all relevant raw data, metadata, updates, retests and analyses must be recorded and stored, even if the original equipment has been replaced or upgraded. Throughout, it is essential to be able to demonstrate that no data has been lost, deleted or corrupted.

The RMS solution

The Realtime Monitoring System automatically creates an extensive and complete audit trail, which can easily be accessed and interrogated by authorized system users. This includes, for example, changes to device configuration, alarms, warnings and systems messages, as well as records of user login and actions, device calibration and removal, data gaps and sensor errors.

An overview of all RMS audit trail events can be found in our online manual:
https://service.rotronic.com/manual/.

Consistent

This essentially means that all data, including revisions, should be recorded and managed in a consistent chronological manner, using appropriate timestamps. In practice, data should appear in a consistent format regardless of the point in the process from which it is being accessed. In turn, this requires that data monitoring and collection instruments must conform to common standards and, if necessary, be reconfigured to present data accordingly.

The RMS solution

All time stamps are recorded automatically in UTC time on the SQL database, providing a consistent and inherent secure record, regardless of where the RMS devices are located. The time synchronization of the server, then the devices, is done via the Network Time Protocol (NTP) via the port 123. RMS will monitor the server time and should there be a difference >30s, then RMS will synchronize with the server time (this will be visible within the audit trail). Monitoring of the server time is possible via a system measuring point.

Enduring

Data and paper records must be readily available for lengthy periods – decades in some instances – even after a process or pharmaceutical product has been discontinued. Paper based records will require a secure archival system, while digital records will demand a resilient storage system, with appropriate backup, power protection, cybersecurity and disaster-recovery measures.

The RMS solution

The Realtime Monitoring System is designed to be used within an industry standard Microsoft operating environment, with a high degree of redundancy. The system can be configured around a local server or in the cloud, with the latter being based on an ISO27001 certified facility to ensure complete data integrity and data availability.

For all on-premise customers, the internal IT team should be able to offer the best advice to ensure data availability over a long time period. Data from RMS can easily be exported into a third-party data historian via OPC connectivity.

Available

Data must not only be captured and stored securely, it must also be immediately available and readable by those responsible for process reviews, audits or inspections at any time during the required retention period. This applies equally to current and archived data, and therefore requires an efficient searchable database, plus the use of tamper-resistant electronic file formats.

The RMS solution

The Realtime Monitoring System features user-configurable dashboards and is designed to ensure that all data is easily accessible to authorized users. The system can also be setup to control user access to specific data sets, to extend security and traceability still further.

Data integrity & Pharma 4.0

The recent introduction of Pharma 4.0, based on the established Industry 4.0 methodology and defined by an ISPE special interest group, has highlighted the importance of data integrity in the pharmaceutical manufacturing sector.

In essence, Pharma 4.0 utilizes the power of Big Data – the huge volume of technical and commercial data generated by pharmaceutical manufacturing, process control, monitoring and business systems – to enable processes and systems to be optimized and continuously improved to deliver greater productivity, profitability and business excellence.

Three factors are, however, critical to the effectiveness of Pharma 4.0: data quality, data integrity and data security.

The importance of cybersecurity

Across industry, Big Data is often stored in the Cloud based on services such as IaaS (infrastructure as a service) and SaaS (software as a service). These bring considerable benefits – not least cost savings – but also presents fresh challenges to data security. As a result, it is common to find many pharmaceutical and life sciences companies continuing to use locally based IT structures and systems in order to manage and minimize risk.

Whichever option is chosen, it is nonetheless essential to take a robust approach to cybersecurity, risk management and threat mitigation, and to consider potential dangers from both external and internal sources.

In many respects, the threat to data security from internal sources – either through incompetence or malicious intent – can be harder to regulate, as access to an integrated and plant-wide process control system can be often achieved from multiple points. These include physical access, through product front panel interfaces, or by the use of removeable memory sticks and USB connections, as well as electronic access via network nodes. In each case, the risk is that business-critical data such as process values, recipes, batch conditions and intellectual property can be stolen or corrupted.

Clearly, having robust business-risk and security policies is essential. Following the guidelines of established standards such as ISA/IEC 62443 can be an effective place to start, as these set out best practice and methods of assessing security performance for pharmaceutical companies using automation and control systems.

At a production level, it is also important to control and monitor access to process control, measurement, analysis and reporting devices. One of the key requirements when selecting equipment and instruments should therefore be their security and access-control functions with, as a minimum, password control and hierarchical access levels. For devices that are ultimately connected through a control network to the internet, local firewalls and advanced security control may also be necessary.

Choice of supplier

Given the importance of data integrity, quality and security, it should go without saying that making the right choice of both pharmaceutical manufacturing equipment and supplier is critical.

As we have noted above, production devices such as sensors and monitoring systems must be capable of meeting a number of key criteria: accuracy, reliability, repeatability, data recording, connectivity and comprehensive access control.

Equally important – in many ways, of greater importance – is the choice of supplier. Their knowledge, experience and support services can often make the difference between a secure, efficient and dependable installation and a solution that underperforms.

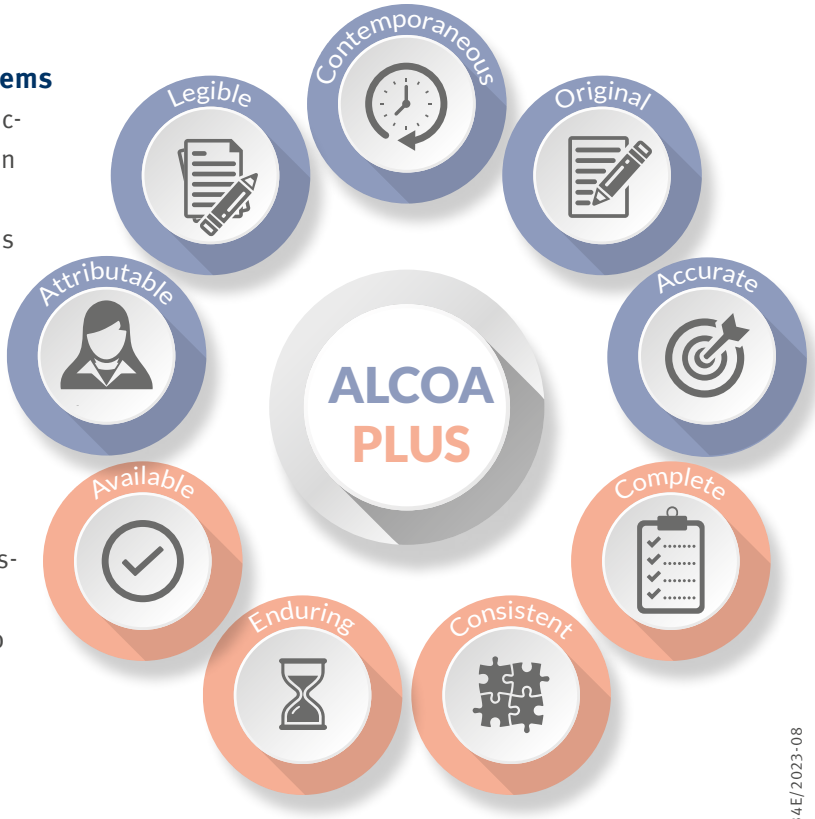
Look for a supplier with proven technologies and products, and a track record or working in the pharmaceutical sector:

- Make sure that they understand your requirements and are able to take a proactive, problem-solving approach.
- Confirm that they are used to working with and, where appropriate, comply with the relevant standards and best practices, such as ALCOA/ALCOA+, GAMP5, ISA/IEC 62443 etc.
- Talk to their existing customers and find out what they think of the suppliers' overall offering.
- Work with their engineering or technical specialists to explore different options to ensure that you have the best possible solution.
- Ensure that they are capable of supporting you as your product requirements change, as well as with additional support services such as equipment recalibration, upgrade or refurbishment.
- Do not simply choose them because they offer the lowest price. This may satisfy your procurement team but will rarely deliver a solution that provides long-term value, security or peace of mind.

ALCOA methodologies & advanced digital systems

As increasing numbers of pharmaceutical manufacturers more to automated and digitized production systems, so the need for greater control and management of ever growing volumes of data becomes increasingly critical.

The ALCOA/ALCOA+ methodologies are a powerful tool that can help to maintain and enhance data quality and integrity, while protecting data security. Combined with the latest generation of advanced process monitoring and analysis equipment, such as the Rotronic RMS, with sophisticated software options, these create an exciting new opportunity for pharmaceutical companies to improve still further the resilience, flexibility and profitability of their production operations.



54034E/2023-08