White Paper

THORNTON
Leading Pure Water Analytics

Data Integrity in Regulated Environments

ALCOA+ for Pharmaceutical Waters

The completeness, consistency and accuracy of data is of ever-growing importance in the pharmaceutical industry. The ALCOA+ framework is designed to ensure data from equipment used in drug manufacturing is of the highest integrity. In respect to sensors for pharmaceutical pure water systems, METTLER TOLEDO provides a tool to help your water system be in compliance with the highest standards for electronic record keeping.

Introduction

We live in a digital world, with access to a vast amount of information that can be accessed from devices as small as a cell phone. This is advantageous; we have instant access to the information we want, also, the need for printed materials (and hence trees to make paper) has been lessened. This reliance on electronic data and records has had a profound effect on scientific information, especially in regulated environments like pharmaceutical manufacturing. Due to the fact that electronic records can be altered or deleted, regulated environments such as pharma/biotech must adhere to strict data integrity regimes to prove that the data they submit to regulatory agencies are complete, accurate, original, etc.

21CFR Part 11 and ALCOA

Parts 210, 211 and 212 of Title 21 of the Code of Federal Regulations (CFR) contain a number of references to data integrity. Many sections include information regarding data integrity-related cGMP requirements for pharmaceutical drugs.

Other regulations that impact data integrity requirements include 21 CFR Part 11, the final rule on Electronic Records and Electronic Signatures, which was released by the FDA in 1997. This regulation defines the criteria in which electronic records and signatures

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Attributable	• Who generated the data? • Who (if anyone) modified it? • What system/instrument generated the data?
Legible	• Data must be readable/legible • Electronic data must be 'readable' by humans
Contemporaneous	• Must be recorded at the time it was created • Cannot be transcribed later • No Post-it notes, no notes on your hand
Original	• All information must be in original format it was created in, preserving accuracy, completeness, content and meaning • Paper printouts are technically not 'original'
Accurate	• Recorded data needs to be accurate and second person verified (when appropriate) • Data in multiple locations need to agree with each other

Table 1

are considered to be trustworthy, reliable and equivalent to paper records. The electronic signature and record keeping requirements specified in 21 CFR Part 11 apply to all FDA-regulated industries, and therefore cover records subject to the requirements set forth in 21 CFR 210, 211 and 212.

The FDA guidance document released in 2016 – Data Integrity and Compliance With cGMP – intends to clarify the current good manufacturing practice (cGMP) regulations for drugs with regards to data integrity. In this revised draft guidance, the FDA clarifies that "For the purpose of this guidance, data integrity refers to the completeness, consistency and accuracy of data"[1]. Therefore, the framework for this data integrity requirement is referred to by its acronym ALCOA, which stands for Attributable, Legible, Contemporaneous, Original and Accurate. Table 1 gives more detail on the individual parts of this framework, including some examples.

Additionally, the United States Pharmacopoeia (USP) maintains the rules and guidance for water quality in the pharmaceutical and cosmetics manufacturing industries in the United States. USP <643> and USP <645> are two key regulations defining total organic carbon (TOC) and conductivity limits for water for injection (WFI) and purified water (PW). These regulations, when coupled to the FDA's Process Analytical Technologies (PAT) initiative, encourages the pharmaceutical industry to use in-process control of quality, rather than utilizing a final test for product quality assurance.

ALCOA and ALCOA+

Beginning in 2019, The World Health Organization (WHO) and other governing bodies requested an update to ALCOA that establishes a more complete definition of data integrity. The resulting framework, ALCOA+, includes additional elements that are now being implemented as recommended by WHO and the International Committee on Harmonization (ICH).

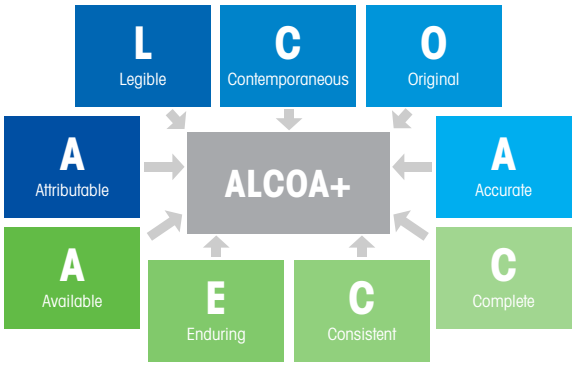


Figure 1

ALCOA+ adds the following four categories: Complete, Consistent, Enduring and Available (Figure 1 and Table 2).

A multi-parameter data integrity solution

In order to meet the requirements of ALCOA+ with regard to electronic record keeping and data integrity for pharmaceutical waters, METTLER TOLEDO Thornton has developed the RecordLOC™ data integrity package.

RecordLOC is a two-part system comprising a PC software tool and a METTLER TOLEDO M800 2-channel, multi-parameter transmitter with 21 CFR Part 11 compatibility. The system can be configured with any combination of two sensors including TOC, conductivity and/or dissolved ozone. RecordLOC provides a transmitter-stored, encrypted, audit trail; however, all user data is stored on the PC to better comply with the ALCOA+ requirement that data is legible, original and contemporaneous.

RecordLOC is unique in that it provides a complete audit trail of TOC as well as conductivity and/or dissolved ozone sensors. This multi-parameter ability is superior to a simple, single-parameter system because it allows users to find and record simultaneous excursions in TOC, conductivity or dissolved ozone, unlike similar solutions that only record TOC and/or conductivity.

Additionally, the solution is based on well-known and trusted METTLER TOLEDO instruments such as the 6000TOCi, UniCond® and pureO_3™ sensors, combined with the M800 transmitter. This provides very high confidence in measurement accuracy and water system control. Additionally, the software on the transmitter and PC tool are multi-language, allowing global organizations to implement the solution anywhere.

More importantly, the M800 transmitter does not store any electronic records or measurement data that could be accidentally manipulated, altered, changed or deleted, therefore meeting the predicate rule requirements of 21 CFR Part 11 and ALCOA+. The M800 transmitter does provide the end-user with the ability to graphically view the measurement parameters over a preselected time period. However, the graphic representation itself is not stored or used for record keeping. For compliant digital record keeping, the M800 transmits electronic

Complete	All recorded data require an audit trail to show nothing has changed
Consistent	Data needs to be chronological (by date stamp)
Enduring	Data must be available long after it was generated (decades)
Available	Data must be accessible, normally achieved with electronic data

Table 2

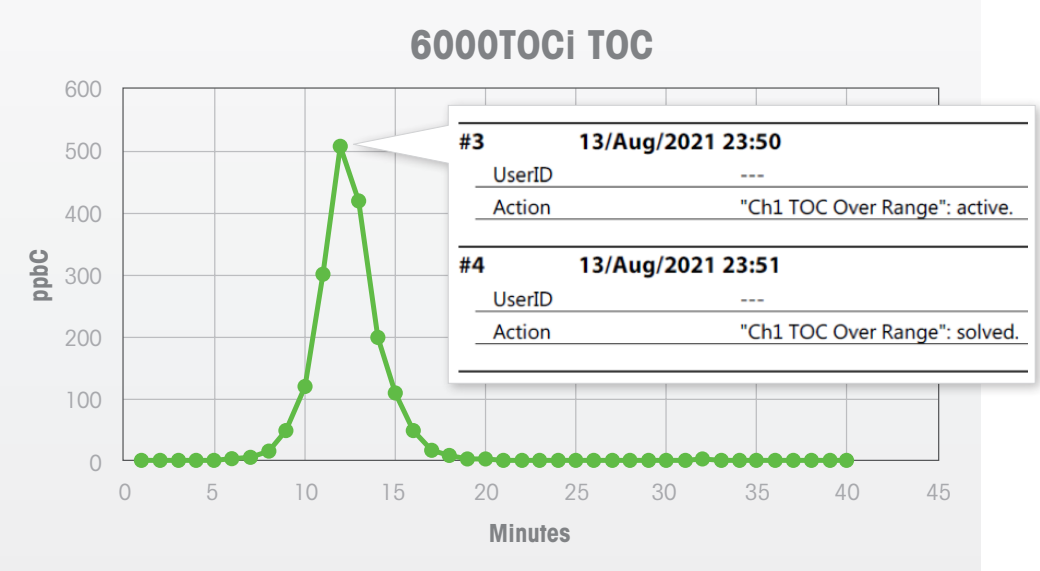


Figure 2: 6000TOCi TOC data showing excursion and audit trail noting the excursion.

data to a PLC, SCADA or Data Collection System (DCS) that meets 21 CFR Part 11 and EC GMP Annex 11 requirements.

RecordLOC also helps users better comply with the FDA's "No added substances" rule, by showing if an excursion in dissolved ozone level has occurred during normal operation, which would violate Part 184 Subpart 1563 of the CFR for addition of antimicrobial agents in water.

Method and experimental results

To simulate a potential excursion on a WFI system used at a pharmaceutical company, a 6000TOCi was plumbed into an ultrapure water (UPW) system, an M800 2-ch 21CFR was connected and the entire system was allowed to rinse-down overnight.

A standard installation qualification (IQ) was performed and the 6000TOCi was calibrated according to the installation instructions. A system suitability test was utilized as a performance qualification (PQ) and a standard addition syringe pump was added to this M800 and 6000TOCi setup. A limit of 500 ppb was defined in the M800 to enable reporting of an excursion. To demonstrate that the system would detect an excursion and also that the audit trail would note the event, two concentrated solutions (50 ppm sucrose and 3.75 mM potassium chloride) were prepared and, through standard addition, added to the water stream.

Figure 2 shows the TOC results (ppb) graphed over time as measured by the 6000TOCi. The 6000TOCi sensor provides real time (one-second interval) measurements, and in the graph, every minute is an average of the measurements over the previous sixty seconds. This degree of data reporting would be impossible with a batch-style instrument. Moreover, the

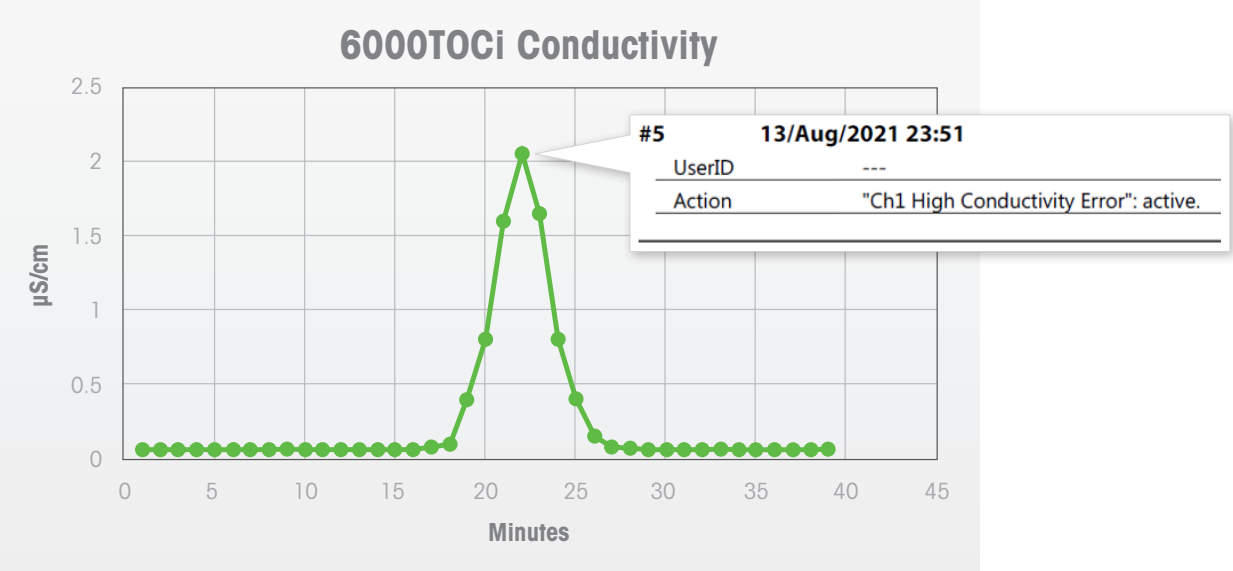


Figure 3: 6000TOCi conductivity data showing excursion and audit trail noting this excursion.

continuous measurements of the 6000TOCi define the complete curve seen in the TOC data. Within the same interval, a batch system that measures every 14 minutes would report one data point at 200 ppb and would therefore not indicate that there had been an excursion.

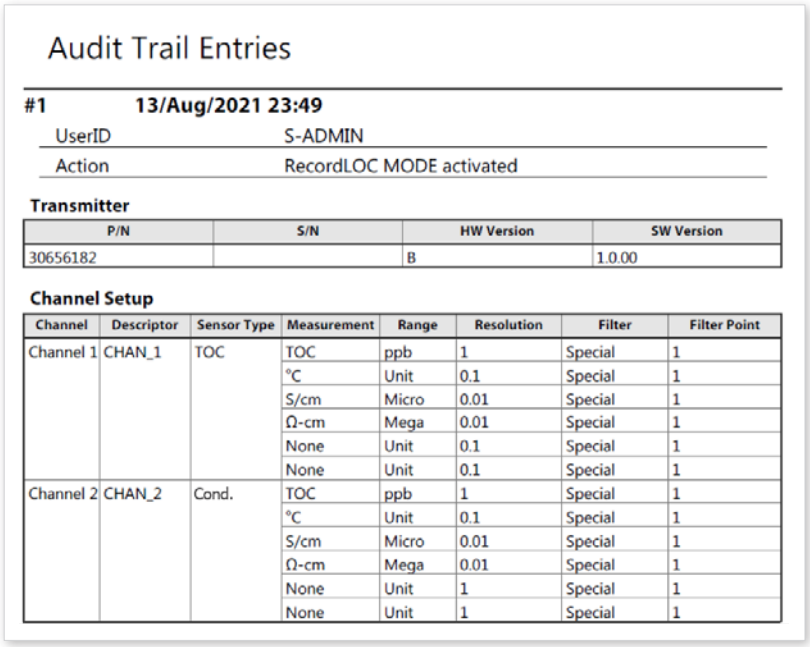
As expected, the 6000TOCi reported the excursion (as per the limit defined in the M800) and the audit trail updated to show the time and date of the >500 ppb excursion (Figure 2).

In a test of the multi-parameter aspect of this system, the same setup was utilized and a high concentration of a potassium chloride salt solution was used to simulate a conductivity excursion. Using standard addition, Figure 3 shows a similar pattern of data including a spike in conductivity to approximately 2 µS/cm at approximately 22 minutes. The audit trail noted the excursion in the water system including the date and time. It should be noted that the insert images are taken from the PDF export of the audit trail, which can be password protected to comply with an organization's quality and reporting standards.

Figure 4 shows a partial audit trail format including the configuration of the transmitter and displays the level of detail that RecordLOC brings to electronic record keeping.

Conclusion

METTLER TOLEDO Thornton's RecordLOC data integrity package, based on the M800 transmitter and well-established sensors such as the 6000TOCi, UniCond or pure$O_{3'}$ offers an easy-to-use, audit-ready system to help facilities become ALCOA+ compliant and conform to the latest regulations for electronic records and reporting. This system helps eliminate paper records for



Audit Trail Entries

#1 13/Aug/2021 23:49

UserID	S-ADMIN
Action	RecordLOC MODE activated

Transmitter

P/N	S/N	HW Version	SW Version
30656182		B	1.0.00

Channel Setup

Channel	Descriptor	Sensor Type	Measurement	Range	Resolution	Filter	Filter Point
Channel 1	CHAN_1	TOC	TOC	ppb	1	Special	1
			°C	Unit	0.1	Special	1
			S/cm	Micro	0.01	Special	1
			Ω-cm	Mega	0.01	Special	1
			None	Unit	0.1	Special	1
			None	Unit	0.1	Special	1
Channel 2	CHAN_2	Cond.	TOC	ppb	1	Special	1
			°C	Unit	0.1	Special	1
			S/cm	Micro	0.01	Special	1
			Ω-cm	Mega	0.01	Special	1
			None	Unit	1	Special	1
			None	Unit	1	Special	1

Figure 4: Audit trail showing setup of the M800 transmitter.

water systems and complies with the fast-moving PAT initiatives set by the FDA.

RecordLOC offers a robust, easy-to-implement, multi-parameter audit trail based on known technology that is truly global with full multilanguage support for multinational organizations.

Water system excursions are noted (time/date stamped) in audit trails for TOC, conductivity and/or dissolved ozone and these records are encrypted (unmodifiable). RecordLOC offers organizations peace-of-mind that their water systems comply with the highest electronic record keeping standards for TOC, conductivity and dissolved ozone.

References

1: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/part-11-electronic-records-electronic-signatures-scope-and-application

www.mt.com/RecordLOC

www.mt.com/pro

For more information

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