

Practical Applications of Data Integrity and Audit Trail Review

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With the prominent rise of electronic systems used in both laboratory and manufacturing processes, companies have been forced to educate staff and develop procedures on the use and management of these systems. For many years there was little guidance on the expectations from auditors on how to ensure that these systems are in compliance and remain that way. Validation is a core part of this guidance and therefore was a primary focus of the systems. As auditors became familiar with the system use and maintenance, general data integrity (DI) became the regulatory and compliance focus. Today, audit trails are a critical focus of DI, and companies must understand the expectations of the review and management of these audit trails.



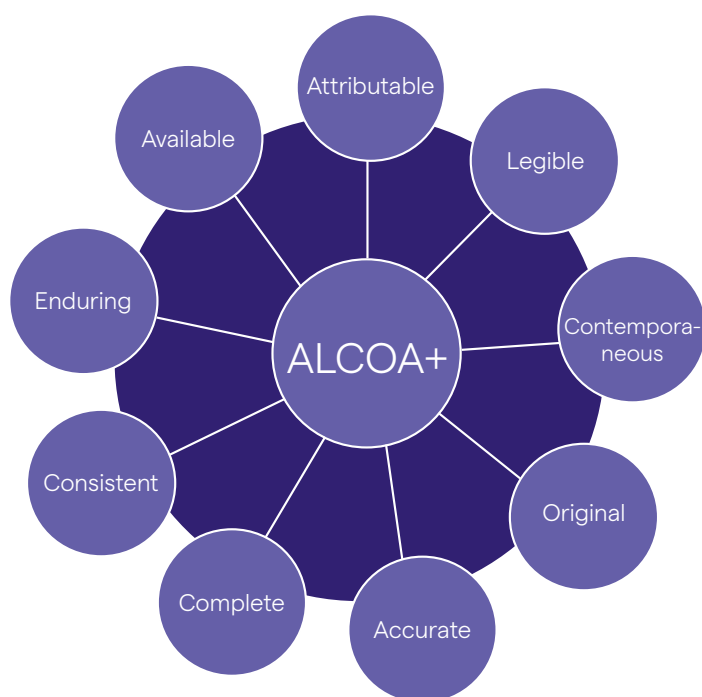


Figure 1.
Overview of ALCOA+ requirements.

Regulatory Guidance

21 CFR Part 11 Subpart B Sec 11.10 Controls for Closed Systems

“Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.”

EudraLex Volume 4 Annex 11: Computerised Systems

“Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated “audit trail”). For change or deletion of GMP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed.”

PIC/S Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments

“Where available, audit trail functionalities for electronic-based systems should be configured properly to capture general system events as well as any activities relating to the acquisition, deletion, overwriting of and changes to data for audit purposes. Audit trails should be verified during validation of the system. Companies should implement procedures that outline their policy and processes for the review of audit trails in accordance with risk management principles.”

FDA Data Integrity and Compliance with CGMP

“Regarding audits, FDA recommends that audit trails that capture changes to critical data be reviewed with each record and before final approval of the record. Audit trails subject to regular review should include, but are not limited to, the following: the change history of finished product test results, changes to sample run sequences, changes to sample identification, and changes to critical process parameters. FDA recommends routine scheduled audit trail review based on the complexity of the system and its intended use.”

MHRA

“An audit trail provides for secure recording of life-cycle details such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record. An audit trail facilitates the reconstruction of the history of such events relating to the record regardless of its medium, including the “who, what, when and why” of the action. Routine data review should include a documented audit trail review where this is determined by a risk assessment.” many of the pipetting tasks currently performed by laboratory staff and do so with greater precision and flexibility. Utilization of these technologies increases technician productivity, reduces lab data errors, eliminates pipette-related repetitive motion injuries and offers potential throughput increases. Lonza's in-house software development experts have written scripts specifically detailing robotic control code in order to process hundreds of plates daily with minimal intervention.

Current Regulatory Requirements

Expectations today for audit trail entries GAMP 5

guidance Automated – The audit trail entries must be automatically captured by the computer system whenever an electronic record is created, modified or deleted.

Secure – Audit trail data must be stored in a secure manner and must not be editable by any user.

Contemporaneous – Each audit trail entry must be time stamped according to a controlled clock which cannot be altered. The time should either be based on central server time or a local time, so long as it is clear in which time zone the entry was performed.

Traceable – Each audit trail entry must be attributable to the individual responsible for the direct data input. Updates made to data records must not obscure previous values and where required by regulation the reason for changing the data must also be recorded.

Maintained – The audit trail must be retained as long as the electronic record is required to be stored.

Available – The audit trail must be available for agency review and copying.

Identification of the user making the entry – This is needed to ensure traceability. This could be a user's unique ID, however there should be a way of correlating this ID to the person.

Date and time stamp – This is a critical element in documenting a sequence of events and vital to establishing an electronic record's trustworthiness and reliability. It can also be effective deterrent to records falsification.

Link to record – This is needed to ensure traceability. This could be the record's unique ID.

Original value - new value – This is needed in order to be able to have a complete history and to be able to reconstruct the sequence of events.

Reason for change – This is only required if stipulated by the regulations pertaining to the audit trailed record.

System Audit Trail vs Data Audit Trail

System audit trail – The system audit trail is comprised of settings that are applied to the system or logs that capture activity or communication.

```
4/3/2019 9:47:15 AM [Info] RecordAuditTrailEntry
4/3/2019 9:47:16 AM [Info] GetUserPrincipal(): expiration is: 57 days 5 hours 14 minutes 9 seconds
4/3/2019 3:48:29 PM [Info] RecordAuditTrailEntry
4/3/2019 3:48:30 PM [Info] GetUserPrincipal(): expiration is: 56 days 23 hours 12 minutes 55 seconds
4/3/2019 3:50:58 PM [Info] RecordAuditTrailEntry
4/3/2019 3:50:58 PM [Info] GetUserPrincipal(): expiration is: 56 days 23 hours 10 minutes 27 seconds
4/3/2019 3:51:02 PM [Info] GetLookupData() called with user: MODADMIN and startDateRange: 1/1/0001 12:00:00 AM
4/3/2019 3:51:02 PM [Warn] ReferenceDataService: startDateRange was NULL.
4/3/2019 3:51:02 PM [Warn] ReferenceDataService: startDateRange was NULL.
4/3/2019 3:51:02 PM [Debug] LookupData: GetObjectData() called.
4/3/2019 3:51:02 PM [Debug] ReferenceDataService: GetLookupData: Elapsed time to get data: 0 min 0 sec
4/3/2019 3:51:03 PM [Info] RecordAuditTrailEntry
4/3/2019 3:51:03 PM [Info] GetUserPrincipal(): expiration is: 56 days 23 hours 10 minutes 21 seconds
4/3/2019 3:51:03 PM [Info] GetTestData() called with user: MODADMIN and startDateRange: 1/1/0001 12:00:00 AM
4/3/2019 3:51:04 PM [Info] GetSampleData() called with user: MODADMIN and startDateRange: 1/1/0001 12:00:00 AM
4/3/2019 3:51:04 PM [Info] GetLocationsData() called with user: MODADMIN and startDateRange: 1/1/0001 12:00:00 AM
4/3/2019 3:51:04 PM [Info] GetResultsData() called with user: MODADMIN and startDateRange: 1/1/0001 12:00:00 AM
4/3/2019 3:51:04 PM [Info] GetOrganismData() called with user: MODADMIN and startDateRange: 1/1/0001 12:00:00 AM
4/3/2019 3:51:04 PM [Warn] ReferenceDataService: startDateRange was NULL.
4/3/2019 3:51:04 PM [Warn] ReferenceDataService: startDateRange was NULL.
4/3/2019 3:51:04 PM [Info] GetUserData() called with user: MODADMIN and startDateRange: 1/1/0001 12:00:00 AM
4/3/2019 3:51:04 PM [Warn] ReferenceDataService: startDateRange was NULL.
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4/3/2019 3:51:04 PM [Warn] ReferenceDataService: startDateRange was NULL.
4/3/2019 3:51:04 PM [Warn] ReferenceDataService: startDateRange was NULL.
4/3/2019 3:51:04 PM [Debug] LimitSql.SelectActive: Elapsed time to get data: 0 min 0 sec
4/3/2019 3:51:04 PM [Debug] ResultsData: GetObjectData() called.
4/3/2019 3:51:04 PM [Debug] LimitRuleGroupSql.SelectActive: Elapsed time to get data: 0 min 0 sec
4/3/2019 3:51:04 PM [Debug] ReferenceDataService: GetResultsData: Elapsed time to get data: 0 min 0 sec
4/3/2019 3:51:04 PM [Debug] LimitRuleSql.SelectActive: Elapsed time to get data: 0 min 0 sec
```

Figure 2.
Example of system audit trail.

Data audit trail – The data audit trail is comprised of information that is applied directly to data i.e. electronic records/results.

Step	Test description	Actual Result	Tester Sign / Date
1.	Record Equipment number and Temperature	Equipment Number <u>146-14001</u> 14602 Temperature <u>45</u> 3601 35	RL 26Feb2019

① Wrong Measurement 26Feb2019 RL
 ② Incorrect Rounding 26Feb2019 RL
 ③ Write over 26Feb2019 RL
 ④ Incorrect Equipment ID 26Feb2019 RL

Data Audit Trail

Figure 3.
Example of data audit trail.

Selecting a System/Remediating a System

The good, the bad and the ugly

Bad – These audit trails are ones that are missing information or ones that utilize files for auditing. Especially if those files are able to be edited (Figure 4).

Ugly – These audit trails have all the necessary information, but it is poorly organized, difficult to search and/or mixed in with logs (Figure 5).

Good – These audit trails give clear visibility into change. Typically, they will clearly identify changes to the user. They will have tools for searching and facilitate a timely review (Figure 6).

Name	Date modified	Type
AutoArchive.pdf	-2018 15:33	Adobe Acrobat
AutoArchive.pdf	-2018 00:01	Adobe Acrobat
AutoArchive.pdf	-2018 00:01	Adobe Acrobat
AutoArchive.pdf	-2018 00:01	Adobe Acrobat
AutoArchive.pdf	-2018 00:01	Adobe Acrobat
AutoArchive.pdf	-2018 00:01	Adobe Acrobat
AutoArchive.pdf	-2018 00:01	Adobe Acrobat
AutoArchive.pdf	-2018 00:01	Adobe Acrobat
AutoArchive.pdf	-2018 00:01	Adobe Acrobat
AutoArchive.pdf	-2018 00:01	Adobe Acrobat
AutoArchive.pdf	-2018 00:01	Adobe Acrobat
AutoArchive.pdf	-2018 00:01	Adobe Acrobat
AutoArchive.pdf	-2018 00:01	Adobe Acrobat
AutoArchive.pdf	-2018 00:01	Adobe Acrobat

Figure 4.
Bad audit trail.

Audit ID	Table Name	Primary ID	User Name	Activity Date	Column 5
419	TIME_FRAME_T	419	MODADMIN	7/2/2015 2:36:51 PM	DESCRIPTION

Audit ID	Table Name	Primary ID	User Name	Activity Date	Column 5
419	TIME_FRAME_T	419	MODADMIN	7/2/2015 2:36:51 PM	DESCRIPTION
Column 1	DESCRIPTION	Old Value 1	New Value 1	Sampling	Sampling
Column 2	TEST_TYPE_ID	Old Value 2	New Value 2	590	590
Column 3	TEST_FRAME_ID	Old Value 3	New Value 3	75	75
Column 4	SEQUENCE	Old Value 4	New Value 4	1	1
Column 5	MRN_TIME	Old Value 5	New Value 5	0	0
Column 6	MRN_CYCLE	Old Value 6	New Value 6	0	0
Column 7	MRN_CYCLE	Old Value 7	New Value 7	0	0
Column 8	MRN_CYCLE	Old Value 8	New Value 8	0	0
Column 9	MRN_CYCLE	Old Value 9	New Value 9	0	0
Column 10	MRN_CYCLE	Old Value 10	New Value 10	0	0
Column 11	MRN_CYCLE	Old Value 11	New Value 11	0	0
Column 12	MRN_CYCLE	Old Value 12	New Value 12	0	0
Column 13	MRN_CYCLE	Old Value 13	New Value 13	0	0
Column 14	MRN_CYCLE	Old Value 14	New Value 14	0	0
Column 15	MRN_CYCLE	Old Value 15	New Value 15	0	0
Column 16	MRN_CYCLE	Old Value 16	New Value 16	0	0
Column 17	MRN_CYCLE	Old Value 17	New Value 17	0	0
Column 18	MRN_CYCLE	Old Value 18	New Value 18	0	0
Column 19	MRN_CYCLE	Old Value 19	New Value 19	0	0
Column 20	MRN_CYCLE	Old Value 20	New Value 20	0	0
Column 21	MRN_CYCLE	Old Value 21	New Value 21	0	0
Column 22	MRN_CYCLE	Old Value 22	New Value 22	0	0
Column 23	MRN_CYCLE	Old Value 23	New Value 23	0	0
Column 24	MRN_CYCLE	Old Value 24	New Value 24	0	0
Column 25	MRN_CYCLE	Old Value 25	New Value 25	0	0
Column 26	MRN_CYCLE	Old Value 26	New Value 26	0	0
Column 27	MRN_CYCLE	Old Value 27	New Value 27	0	0
Column 28	MRN_CYCLE	Old Value 28	New Value 28	0	0
Column 29	MRN_CYCLE	Old Value 29	New Value 29	0	0
Column 30	MRN_CYCLE	Old Value 30	New Value 30	0	0

Figure 5.
Ugly audit trail.

	00000YHK	10/27/2017 9:30:37 AM	R1001.1	Air Viable	Global Pharmaceutical...	MODADMIN
	00000YJ1	10/9/2017 1:16:11 PM	R1003.501a	MAS Air Viable 1 Stage...	Global Pharmaceutical...	MODADMIN
Remaining minutes until samples complete: 0						
Table Notes						
	Operation	Note	User Name		Note Date	
	SAMPLE	The result was changed from 300 to 100 because Rob can't count	MODADMIN		10/4/2017 10:21:26 AM	
	SAMPLE	Added TW Number	MODADMIN		10/11/2017 4:03:03 PM	
	RESULT	Submitted by Accugenix Import	MODADMIN		10/27/2017 9:30:38 AM	
Sampling Incubation Testing Readings Excursions Exceeded Limits Media Equipment E-Sigs Organism Reviews Table Notes Group						
Readings History						
Drag a column header here to group by that column.						
	Measurement	Operator	Value	Uom	Reading Date	Performed User Audit Action Audit Date
	Bacteria	=	300	cfu	10/4/2017 9:56:48 AM	MODADMIN I 10/4/2017 10:01:14 AM
	TSA Mold	=	0	cfu	10/4/2017 9:56:48 AM	MODADMIN I 10/4/2017 10:01:14 AM
	TSA Count	=	300	cfu	10/4/2017 9:56:48 AM	MODADMIN I 10/4/2017 10:01:14 AM
	TSA Probable Count	=	TNTC	cfu/m^3	10/4/2017 9:56:48 AM	MODADMIN I 10/4/2017 10:01:14 AM
	TSA Total Count	=	TNTC	cfu/m^3	10/4/2017 9:56:48 AM	MODADMIN I 10/4/2017 10:01:14 AM
	Bacteria	=	100	cfu	10/4/2017 9:56:48 AM	MODADMIN U 10/4/2017 10:21:52 AM
	TSA Mold	=	0	cfu	10/4/2017 9:56:48 AM	MODADMIN U 10/4/2017 10:21:52 AM
	TSA Count	=	100	cfu	10/4/2017 9:56:48 AM	MODADMIN U 10/4/2017 10:21:52 AM
	TSA Probable Count	=	124	cfu/m^3	10/4/2017 9:56:48 AM	MODADMIN U 10/4/2017 10:21:52 AM
	TSA Total Count	=	124	cfu/m^3	10/4/2017 9:56:48 AM	MODADMIN U 10/4/2017 10:21:52 AM
Readings History Dilution History Dilution Equipment History Incubation History Organism Found History Sample History Workspace Equip						

Figure 6.
Good audit trail.

System review and remediation

System review is essential for identifying and remediating critical gaps in your systems. There should be a review of the system capabilities against current audit trail expectations to document any gaps in functionality. Once that review occurs an evaluation of remediation options can be executed. This could include upgrades to existing software, utilizing third party auditing tools or system replacement. System replacement allows a bottom up approach to ensuring the system has adequate audit trail controls in place. This process should start before a system is selected as part of a request for proposal (RFP) process. The finalized user requirements specification (URS) that comes out of the RFP process will allow you to define good audit trail requirements up front. Based on the URS, design documents are created that should clearly identify where the audit trail resides, necessary parameters, usability, viewability, searching and sorting information and most importantly the design controls. These will outline its ability to be turned off and its ability to capture all actions in the system.

Audit trail review

General guidelines dictate that the system must be validated first. Define which data is critical to patient safety and regulatory compliance. Analyze the path of data in the system and the business process, specifically looking at the critical data. Identify areas of high risk to patient safety and compliance. Develop risk-based approach based on criticality of data. Ultimately, the audit trail review is dictated by the type of audit trail. For the system audit trail, it should be reviewed periodically based on risk. The

goal is to focus on anything with direct impact to product or release via failure mode and effects analysis (FMEA). This can be very specific for a company because it ensures changes of master data, configuration, interfaced devices/systems, infrastructure or settings. If the system lacks certain controls, making changes requires significantly more verification steps to ensure the change was made appropriately. For the data audit trail, it should be reviewed as part of regular review, prior to batch disposition. It also needs to be an integrated part of the approval process, which is clearly outlined in a procedure.

Audit trail tools

The mechanics of review are based upon a risk assessment that is generated for the system. The goal of the risk assessment is to be quantifiable, objective and actionable. It should take into account the possible measures that can be implemented to reduce the risk to data integrity. The FMEA tool is a common and standard way to assess quality control systems. It is a qualitative and systematic tool, usually created within a spreadsheet, to help practitioners anticipate what might go wrong with a product or process. In addition to identifying how a product or process might fail and the effects of that failure, FMEA also helps find the possible causes of failures and the likelihood of failures being detected before occurrence. It provides a framework to consistently assess the risk to data integrity and perform standardized reassessments as the systems and processes change and evolve.

Based upon the outcome of the assessment, procedures defining the frequency and process for audit trail review should be created. Part of this process should include how the evidence of the audit trail review should be captured. This can include the use of tools external to the system, if the system itself does not have adequate capability to do so. And allows for a clear link between the audit trail and its review. Tools to efficiently identify the required Critical Audit Trail Entries should be developed and validated. These can include: validated Excel spreadsheets, validated access data bases (Scripts), customized reports or other validated software (using a validated interface)

Periodic review

This is the scheduled review of the system audit trail. The frequency is based upon the GAMP category and the criticality of the data in the system. It should confirm traceability or documentation of data in the audit trail, for example, deletions, modifications of GxP critical data items, undocumented configuration changes and system access.

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