

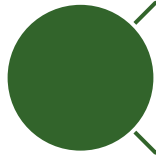
**ThermoFisher**  
S C I E N T I F I C

## Comply with Data Integrity Regulations with Chromeleon CDS Software

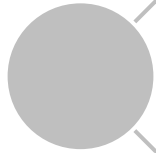
Anna Severoni  
*Sales Support Specialist for Chromatography*  
*Thermo Fisher Scientific, Rodano (MI)*

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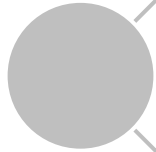
-  Introduction
-  Data integrity
-  Audit trails
-  Record management
-  Summary
-  Questions and answers



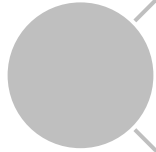
# Introduction



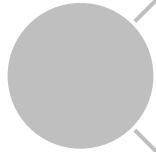
Data integrity



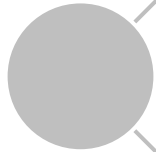
Audit trails



Record management



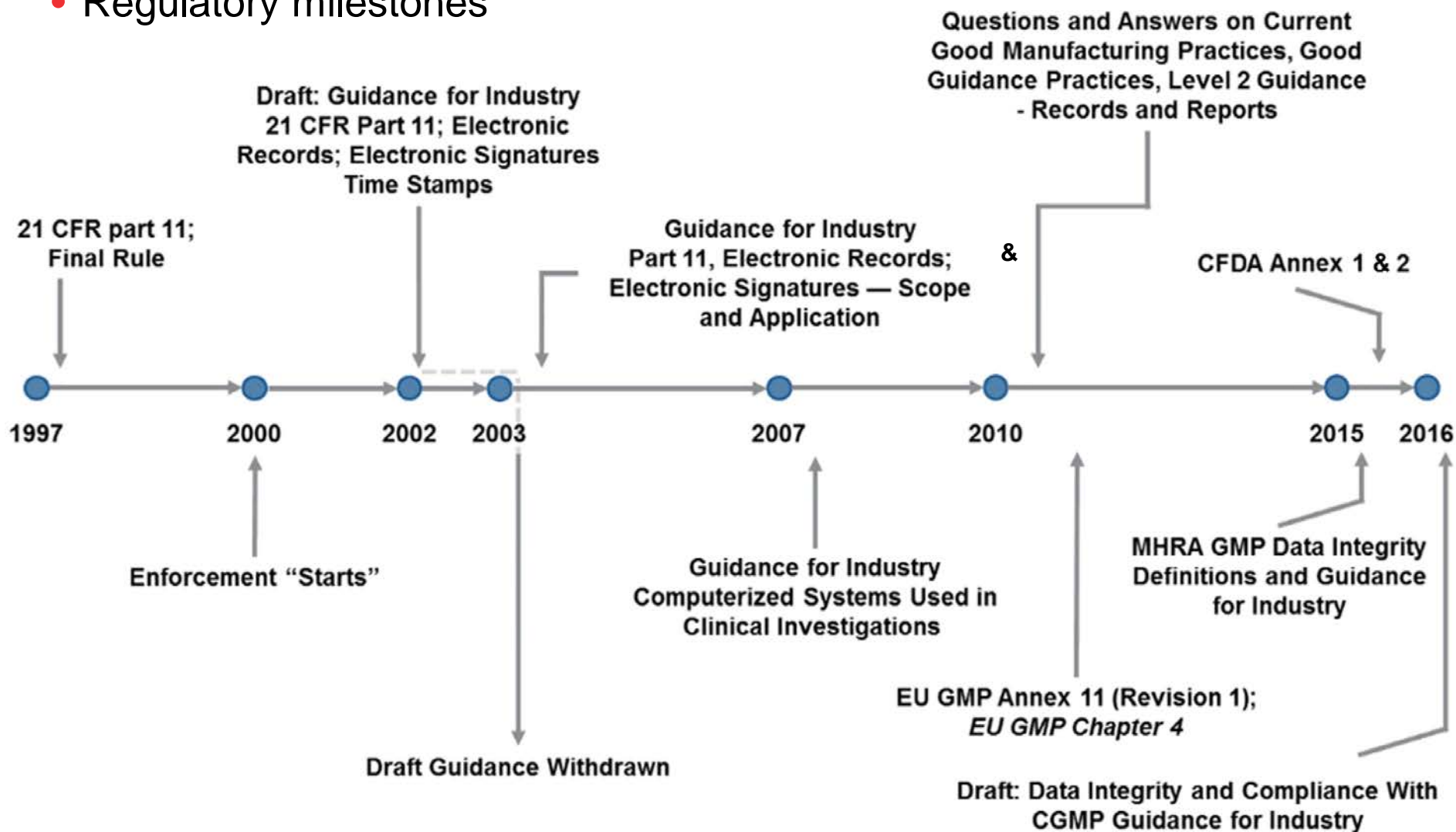
Summary



Questions and answers

# Introduction

- Regulatory milestones



# Introduction

- Data integrity requirements
  - New guidelines in 2015 & 2016 from MHRA, CFDA and FDA
  - Covers authenticity and security of data
  - Clarifies role of data integrity in current good manufacturing practice (CGMP) for drugs
  - Contains current thinking on creation and handling of data in accordance with CGMP requirements
- Software needs to meet regulatory requirements
  - Includes requirements for 21 CFR Part 11 compliance



- In recent years, FDA and MHRA have increased focus on data integrity during CGMP inspections
- Observed CGMP violations involving data integrity during inspections
- Ensuring data integrity is important
  - Industry's responsibility to ensure safety, efficacy, and quality of drugs
  - Regulatory responsibility to protect the public health
- How can Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) software help?

- Introduction
- **Data integrity**
- Audit trails
- Record management
- Summary
- Questions and answers

# Data Integrity

- What is “data integrity”?
  - Completeness, consistency, and accuracy of data

## Attributable

Who performed an action and when?

## Legible

Can you read the data file and written entries throughout the life cycle?

## Contemporaneous

Documented at the time of the activity?

## Original

Original record or a certified copy?

## Accurate

No errors or editing without documented amendments?

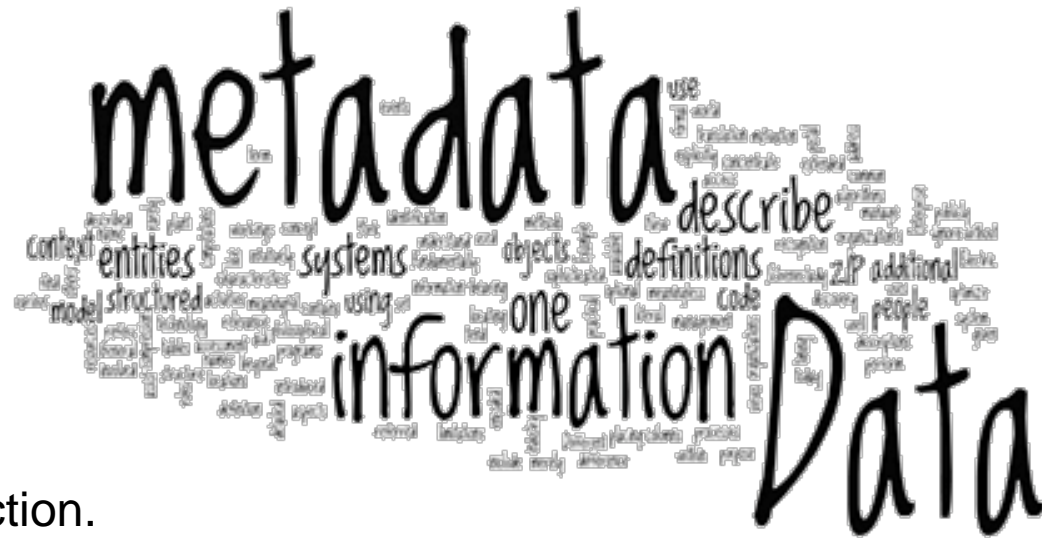
## Use ALCOA+ Criteria for Data Integrity





- What is “data”?
  - Any recorded information
  - 2 types:
    - **Static** - Fixed-data document such as paper record or electronic image
    - **Dynamic** - Record format that allows interaction between user and record content
      - E.g. chromatogram allowing user to change baseline or reprocess data so peaks may change size; user modifiable formulas or entries in spreadsheet

- What is “metadata”?
  - Metadata is data about data
    - Contextual information required to understand data
    - A data value is meaningless by itself without additional information
  - Metadata can describe a single piece of data, a data set or collection.



- Introduction
- Data integrity
- **Audit trails**
- Record management
- Summary
- Questions and answers

- What is an “audit trail”?
  - Secure, computer-generated, time-stamped electronic record that allows for reconstruction of events relating to creation, modification, or deletion of an electronic record
  - Electronic audit trails include those that track creation, modification, or deletion of data **and** those that track actions at the record or system level.
  - CGMP-compliant record-keeping practices prevent data from being lost or obscured. Electronic record-keeping systems, which include audit trails, **can** fulfil these CGMP requirements.



*Chronology of the “who, what, when, and why” of a record*

- Is it acceptable to only save final results from reprocessed laboratory chromatography?
  - No. analytical methods should be capable and stable
  - For most lab analyses, reprocessing data should not be regularly needed
  - If chromatography is reprocessed, written procedures must be established and followed and each result retained for review
  - Must have complete data in lab records, which includes raw data, graphs, charts, and spectra from lab instruments
- Predicated rules show this refers to reprocessing of **samples**, not **data**.
  - Must keep all data (and metadata) relating to each analysis
  - Versioning helps track changes to objects

# Audit Trails in Chromeleon CDS

Chromeleon CDS provides industry-leading audit trails.

- Detailed audit trails for:
  - Chromeleon console and chromatography studio
  - Administration console, instrument configuration manager, data vault manager
  - Chromeleon CDS station
- Logs all user, instrument and system actions
  - E.g. user logon/logoff, instrument setup, sequence start/stop, data processing, admin changes, services startup/shutdown, etc.

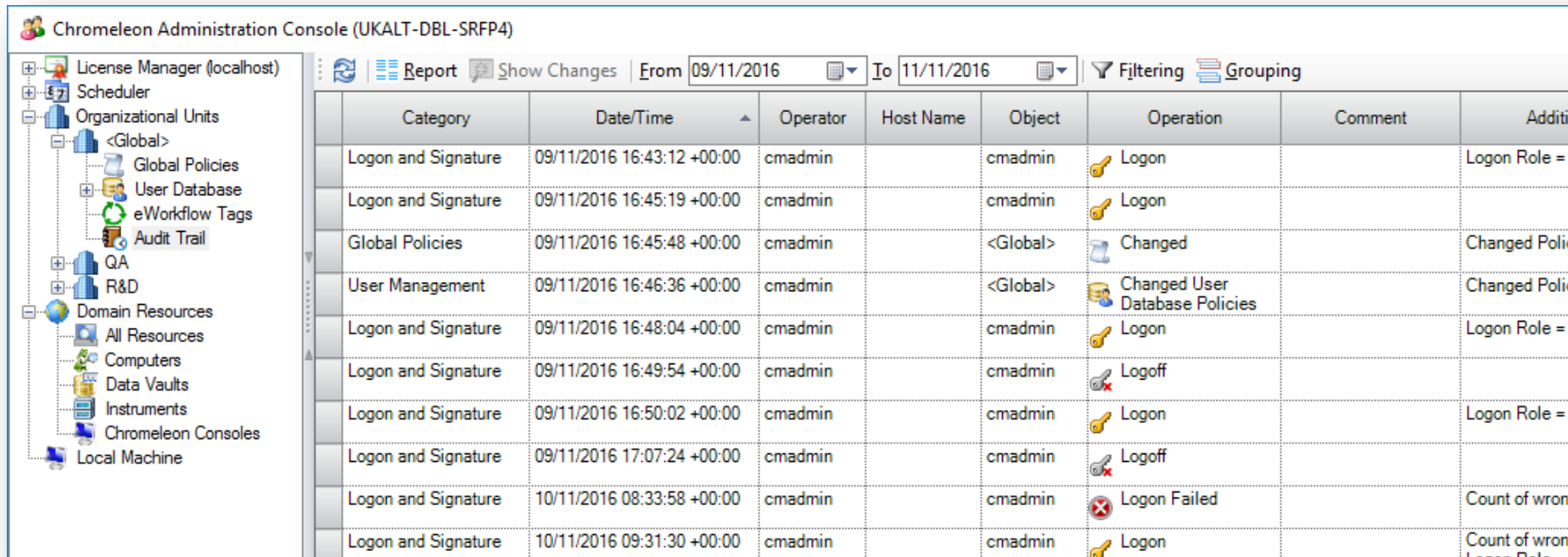
Name	Type	Version	Date / Time	Operator	Operation	Comment	Additional Information
ChromeleonLocal	Data Vault	1	10/11/2016 12:32:43 +00:00	cmadmin	Changed	Lockout other users	Access control changed
ChromeleonLocal	Data Vault	1	10/11/2016 10:09:57 +00:00	cmadmin	Changed		Enable versioning and data audit trails.
Instrument Utilization	Folder	1	12/09/2016 14:04:39 +01:00	cmadmin	Created		Imported from C:\Users\darrenb\Desktop

Category	Date/Time	Operator	Host Name	Object	Operation
User Management	10/11/2016 09:53:46 +00:00	cmadmin		Full Access	Changed Role
Logon and Signature	10/11/2016 09:54:04 +00:00	cmadmin		cmadmin	Logoff
Logon and Signature	10/11/2016 09:54:14 +00:00	cmadmin		cmadmin	Logon

# Audit Trails in Chromeleon CDS

- Chromeleon CDS consolidated audit trail viewer
  - Combines all audit trails within organizational unit
  - Events are categorized for filtering and grouping
  - Entries contain significant detail



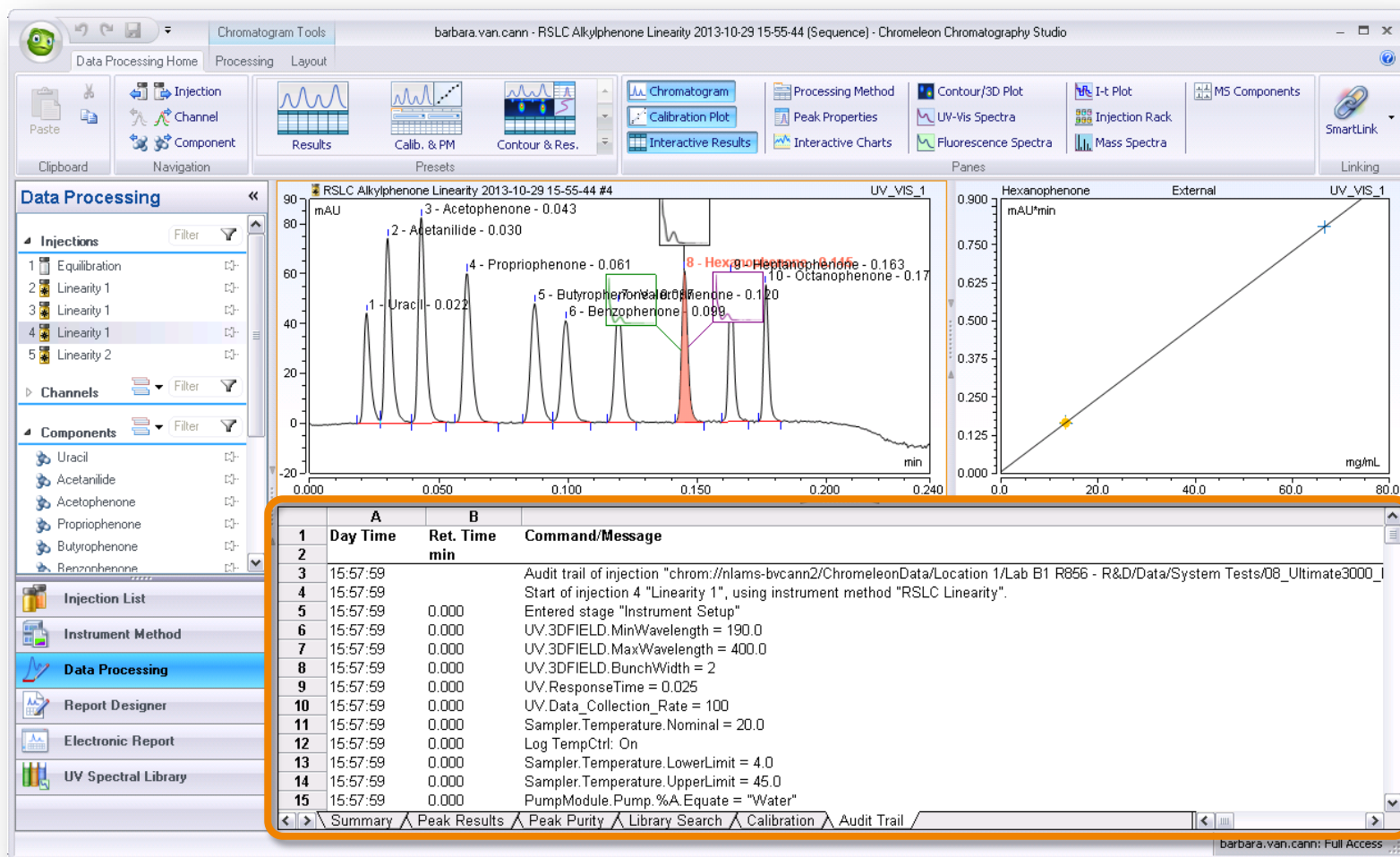
Chromeleon Administration Console (UKALT-DBL-SRFP4)

Report Show Changes From 09/11/2016 To 11/11/2016 Filtering Grouping

Category	Date/Time	Operator	Host Name	Object	Operation	Comment	Additi
Logon and Signature	09/11/2016 16:43:12 +00:00	cmadmin		cmadmin	Logon		Logon Role =
Logon and Signature	09/11/2016 16:45:19 +00:00	cmadmin		cmadmin	Logon		
Global Policies	09/11/2016 16:45:48 +00:00	cmadmin		<Global>	Changed		Changed Poli
User Management	09/11/2016 16:46:36 +00:00	cmadmin		<Global>	Changed User Database Policies		Changed Poli
Logon and Signature	09/11/2016 16:48:04 +00:00	cmadmin		cmadmin	Logon		Logon Role =
Logon and Signature	09/11/2016 16:49:54 +00:00	cmadmin		cmadmin	Logoff		
Logon and Signature	09/11/2016 16:50:02 +00:00	cmadmin		cmadmin	Logon		Logon Role =
Logon and Signature	09/11/2016 17:07:24 +00:00	cmadmin		cmadmin	Logoff		
Logon and Signature	10/11/2016 08:33:58 +00:00	cmadmin		cmadmin	Logon Failed		Count of wron
Logon and Signature	10/11/2016 09:31:30 +00:00	cmadmin		cmadmin	Logon		Count of wron

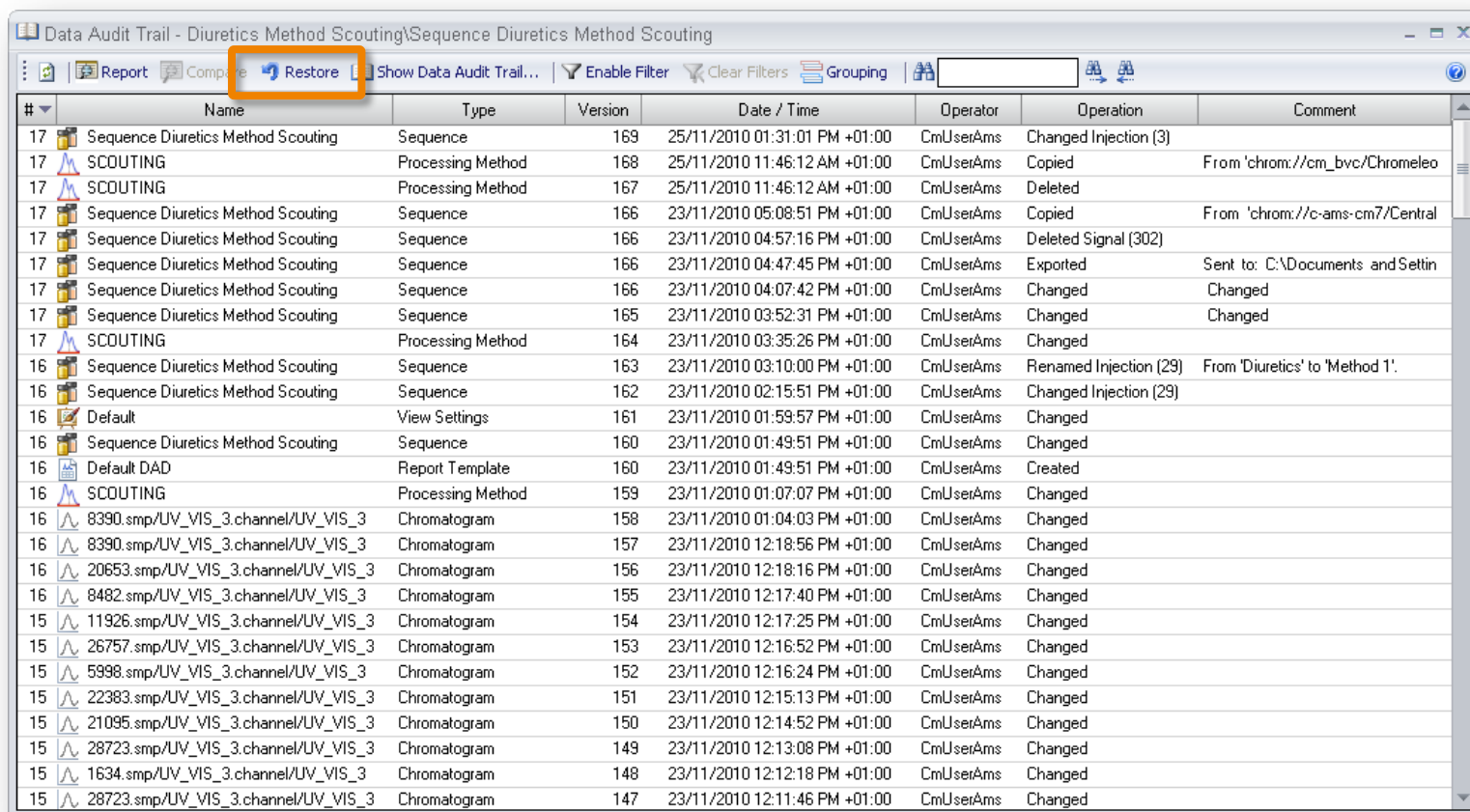
# Audit Trails in Chromeleon CDS

- Instrument daily event audit trail for each injection



# Audit Trails in Chromeleon CDS

- Modification history audit trail
  - Displays complete change history of each object (versions)
  - Can roll back (restore) a previous version



#	Name	Type	Version	Date / Time	Operator	Operation	Comment
17	Sequence Diuretics Method Scouting	Sequence	169	25/11/2010 01:31:01 PM +01:00	CmUserAms	Changed Injection (3)	
17	SCOUTING	Processing Method	168	25/11/2010 11:46:12 AM +01:00	CmUserAms	Copied	From 'chrom://cm_bvc/Chromeleo
17	SCOUTING	Processing Method	167	25/11/2010 11:46:12 AM +01:00	CmUserAms	Deleted	
17	Sequence Diuretics Method Scouting	Sequence	166	23/11/2010 05:08:51 PM +01:00	CmUserAms	Copied	From 'chrom://c-ams-cm7/Central
17	Sequence Diuretics Method Scouting	Sequence	166	23/11/2010 04:57:16 PM +01:00	CmUserAms	Deleted Signal (302)	
17	Sequence Diuretics Method Scouting	Sequence	166	23/11/2010 04:47:45 PM +01:00	CmUserAms	Exported	Sent to: C:\Documents and Settin
17	Sequence Diuretics Method Scouting	Sequence	166	23/11/2010 04:07:42 PM +01:00	CmUserAms	Changed	Changed
17	Sequence Diuretics Method Scouting	Sequence	165	23/11/2010 03:52:31 PM +01:00	CmUserAms	Changed	Changed
17	SCOUTING	Processing Method	164	23/11/2010 03:35:26 PM +01:00	CmUserAms	Changed	
16	Sequence Diuretics Method Scouting	Sequence	163	23/11/2010 03:10:00 PM +01:00	CmUserAms	Renamed Injection (29)	From 'Diuretics' to 'Method 1'.
16	Sequence Diuretics Method Scouting	Sequence	162	23/11/2010 02:15:51 PM +01:00	CmUserAms	Changed Injection (29)	
16	Default	View Settings	161	23/11/2010 01:59:57 PM +01:00	CmUserAms	Changed	
16	Sequence Diuretics Method Scouting	Sequence	160	23/11/2010 01:49:51 PM +01:00	CmUserAms	Changed	
16	Default DAD	Report Template	160	23/11/2010 01:49:51 PM +01:00	CmUserAms	Created	
16	SCOUTING	Processing Method	159	23/11/2010 01:07:07 PM +01:00	CmUserAms	Changed	
16	8390.smp/UUV_VIS_3.channel/UUV_VIS_3	Chromatogram	158	23/11/2010 01:04:03 PM +01:00	CmUserAms	Changed	
16	8390.smp/UUV_VIS_3.channel/UUV_VIS_3	Chromatogram	157	23/11/2010 12:18:56 PM +01:00	CmUserAms	Changed	
16	20653.smp/UUV_VIS_3.channel/UUV_VIS_3	Chromatogram	156	23/11/2010 12:18:16 PM +01:00	CmUserAms	Changed	
16	8482.smp/UUV_VIS_3.channel/UUV_VIS_3	Chromatogram	155	23/11/2010 12:17:40 PM +01:00	CmUserAms	Changed	
15	11926.smp/UUV_VIS_3.channel/UUV_VIS_3	Chromatogram	154	23/11/2010 12:17:25 PM +01:00	CmUserAms	Changed	
15	26757.smp/UUV_VIS_3.channel/UUV_VIS_3	Chromatogram	153	23/11/2010 12:16:52 PM +01:00	CmUserAms	Changed	
15	5998.smp/UUV_VIS_3.channel/UUV_VIS_3	Chromatogram	152	23/11/2010 12:16:24 PM +01:00	CmUserAms	Changed	
15	22383.smp/UUV_VIS_3.channel/UUV_VIS_3	Chromatogram	151	23/11/2010 12:15:13 PM +01:00	CmUserAms	Changed	
15	21095.smp/UUV_VIS_3.channel/UUV_VIS_3	Chromatogram	150	23/11/2010 12:14:52 PM +01:00	CmUserAms	Changed	
15	28723.smp/UUV_VIS_3.channel/UUV_VIS_3	Chromatogram	149	23/11/2010 12:13:08 PM +01:00	CmUserAms	Changed	
15	1634.smp/UUV_VIS_3.channel/UUV_VIS_3	Chromatogram	148	23/11/2010 12:12:18 PM +01:00	CmUserAms	Changed	
15	28723.smp/UUV_VIS_3.channel/UUV_VIS_3	Chromatogram	147	23/11/2010 12:11:46 PM +01:00	CmUserAms	Changed	



# Audit Trails in Chromeleon CDS

- Version comparison tool

Compare Instrument Method 'UltiMate3000' version 1 with version 2

Version	Date / Time	Operator	Client Computer
1	02/12/2009 13:02:38	SQuinn	L-GERSQUINN
2	02/12/2009 13:03:44	SQuinn	L-GERSQUINN

Visualization Options  
 Complete  
 Only Changes

Property Name	Value version 1	Value version 2
Comment	UltiMate3000	UltiMate3000
Instrument Server	L-GERSQUINN	L-GERSQUINN
Instrument	05_UltiMate3000_1	05_UltiMate3000_1

**Change**

**Version 1**

Time	Symbol	Value	Comment
Initial Time	Instrument Setup		
	Sampler.InjectMode	Normal	
	Sampler.PumpDevice	"Pump"	
	Sampler.SyncWithPump	On	
	Pump.MaximumFlowRampDown	1.000 [ml/min <sup>2</sup> ]	
	Pump.MaximumFlowRampUp	1.000 [ml/min <sup>2</sup> ]	
	Pump.%B.Equate	"Acetonitrile"	
	Pump.%C.Equate	"Methanol"	
	Pump.Pressure.UpperLimit	400 [bar]	
0.00	Inject Preparation		
0.00	Inject		
0.00	Start Run		
	UV.UV_VIS_1.AcqOn		
0.00	Run		
	Pump.Flow	1.000 [ml/min]	
8.00	Pump.Flow	2.000 [ml/min]	
8.00	Stop Run		
	UV.UV_VIS_1.AcqOff		

**Deletion**

**Version 2**

Time	Symbol	Value	Comment
Initial Time	Instrument Setup		
	Sampler.InjectMode	Normal	
	Sampler.PumpDevice	"Pump"	
	Sampler.SyncWithPump	On	
	Pump.MaximumFlowRampDown	1.000 [ml/min <sup>2</sup> ]	
	Pump.MaximumFlowRampUp	1.000 [ml/min <sup>2</sup> ]	
	Pump.%A.Equate	"0.1M Phosphate Buffer"	
	Pump.Pressure.UpperLimit	400 [bar]	
	Pump.%B.Equate	"Acetonitrile"	
	UV.UV_VIS_1.Wavelength	280.0 [nm]	
0.00	Inject Preparation		
0.00	Inject		
0.00	Start Run		
	Pump.Pump_Pressure.AcqOff		
0.00	Run		
	Pump.Flow	2.000 [ml/min]	
8.00	Pump.Flow	2.000 [ml/min]	
8.00	Stop Run		
	UV.UV_VIS_1.AcqOff		
	Pump.Pump_Pressure.AcqOff		

**Addition**

# Audit Trails in Chromeleon CDS

- File section in injection list and folder view shows current version

cmadmin - Chromeleon Console

Back Create File Edit View Tools Help

Data

Name	Type	Date Modified	Version	Comment
Station Qual 2016-11-10	Sequence	10/11/2016 09:49:51 +00:00	1	Sequence for Station Operational Qualification

Folder 'Runs' selected

cmadmin - Chromeleon Console

Back Create File Edit View Tools Help

Data

Run Finished

#	UV_VIS_1	Name	Type	Level	Position	Volume [µl]	Instrument Method
1		Alkylphenones 1	Calibration Standard	01	RA1	2.000	CM_OQ
2		Alkylphenones 2	Calibration Standard	01	RA1	4.000	CM_OQ
3		Alkylphenones 3	Calibration Standard	01	RA1	8.000	CM_OQ
4		Alkylphenones 4	Calibration Standard	01	RA1	12.000	CM_OQ
5		Alkylphenones 5	Calibration Standard	01	RA1	16.000	CM_OQ
6		Alkylphenones 6	Calibration Standard	01	RA1	20.000	CM_OQ
7		Alkylphenones 7	Unknown		RA2	4.000	CM_OQ

Click here to add a new injection

Name	Type	Date Modified	Version	Comment
CM_OQ	Processing Method	10/11/2016 09:49:19 +00:00	1	
CM_OQ	Instrument Method	10/11/2016 09:49:51 +00:00	1	
CM_OQ	Report Template	10/11/2016 09:49:19 +00:00	1	
CM_OQ	View Settings	10/11/2016 09:49:19 +00:00	1	

Associated Items Custom Sequence Variables (0) Custom Formulas

Sequence 'Station Qual 2016-11-10' selected cmadmin: Full Access

# Audit Trails in Chromeleon CDS

- Privileged actions
  - Require authorization for specified actions
  - Ensure users add appropriate comments for specified actions
  - Use standardized comments or free entry

The screenshot displays the Chromeleon Administration Console (UKALT-DBL-SRFP4) with the 'Privileged Actions' configuration window open. The 'List of policies' section shows various actions, with 'Privileged Actions' highlighted. The 'Settings' tab is active, showing a checked box for 'Allow separate policy settings for Organizational Units'. A table lists actions such as 'Instrument Configuration', 'Instrument Method', 'Create', 'Delete', 'Modify', 'Copy', 'Move', 'Rename', 'Instrument Audit Trail', 'Data Vault', and 'Folder'. An 'Authorization and Comment Required' dialog box is overlaid on top, featuring the Chromeleon 7 logo and the title 'Authorization and Comment'. The dialog contains fields for 'User Name' (cmadmin), 'Logon Password' (masked), and a 'Comment' field with the text 'Created new user for demo purposes'. The 'Comment' field has a character count of '221 characters remaining'. Buttons for 'OK', 'Cancel', and 'Help' are at the bottom.

Action
Instrument Configuration
Instrument Method
Create
Delete
Modify
Copy
Move
Rename
Instrument Audit Trail
Data Vault
Folder

- Introduction
- Data integrity
- Audit trails
- **Record management**
- Summary
- Questions and answers

*All data should be stored, controlled and archived correctly.*

- When does electronic data become a CGMP record?
  - When generated to satisfy any CGMP requirement, all data becomes a CGMP record
  - Must document, or save, data at time of performance (contemporaneous)
    - E.g. chromatograms should be sent to long-term storage upon run completion
  - Not acceptable to record data on paper that will be discarded after data are transcribed to permanent laboratory notebook
  - Not acceptable to store data electronically in temporary memory, in manner that allows for manipulation, before creating permanent record

*All data should be stored, controlled and archived correctly.*

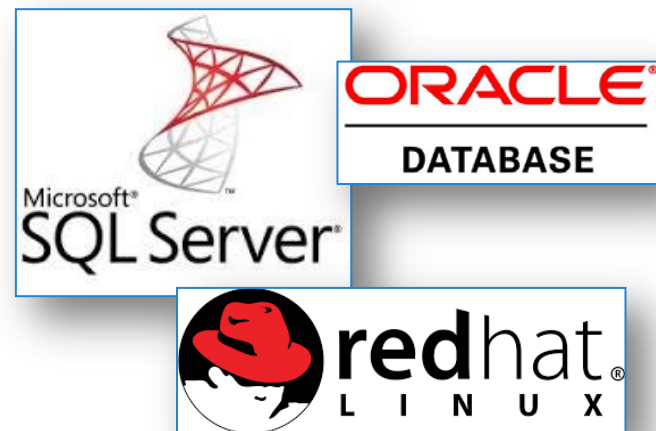
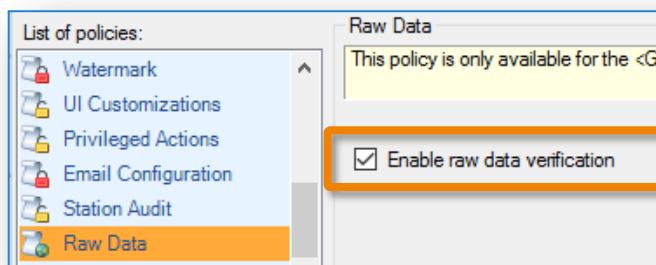
- How do regulatory bodies use the term “backup”?
  - A true copy of original data that is maintained securely throughout records retention period.
  - Backup file should contain data (with associated metadata) in original format or in format compatible with original format.
- Must not be confused with backup copies!
  - Created during normal computer use and temporarily maintained for disaster recovery (e.g. in case of a computer crash or other interruption)
- How does Chromeleon CDS help?



# Record Management – Data Storage

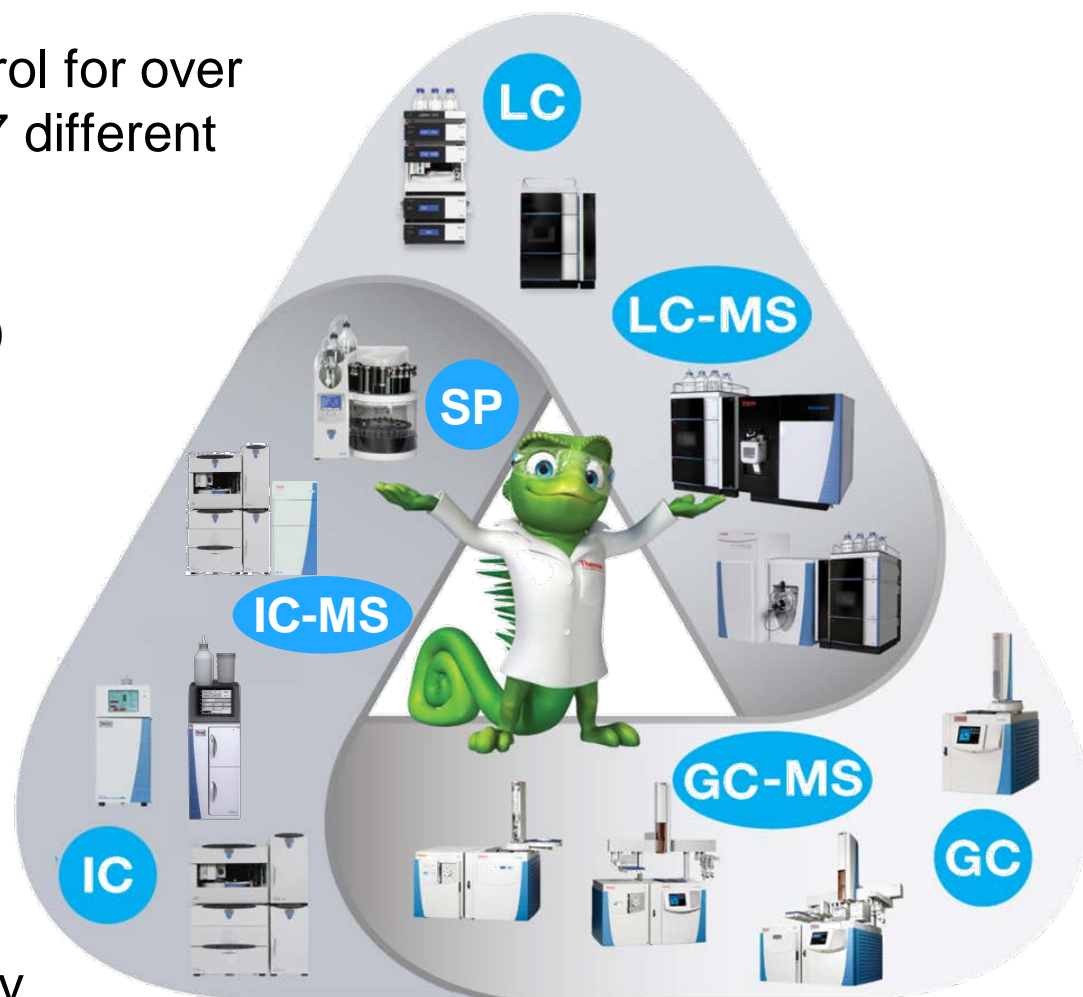
## Immediate transfer to long-term storage

- Chromeleon CDS uses relational database
  - Microsoft® SQL® Server Express (2005 SP3, 2008 R2 SP2 & 2014 SP2)
  - Microsoft® SQL® Server (2008 R2, 2012 & 2014 SP2)
  - Oracle® Database 11g & 12c
  - Oracle® Database 12c on Red Hat® Enterprise Linux® 7
- Detect changes to raw files
  - Automatic detection of raw files being manipulated outside Chromeleon CDS



# Record Management – Data Storage

- Bi-directional instrument control for over 450 different modules from 17 different manufacturers including:
  - Thermo Scientific systems (LC, IC, GC, MS, Sample Prep)
  - Agilent (LC, GC)
  - Waters (LC)
  - Shimadzu (LC, GC)
  - Varian (LC, GC)
  - Perkin Elmer (LC, GC)
  - Gilson (LC)
  - CTC PAL (Sample Prep)
- Highest data transport security
  - Communication secured using latest standards





# Record Management – Data Control

The screenshot displays the Chromeleon 7 software interface. The main window shows an "Electronic Report" for a sequence named "CmServiceAMS - RSLC Alkylphenone Linearity 2013-10-11 10-21-53 (Sequence) - Chromeleon Chromatogr...". The report includes a "Chromatogram and Results" section with a chromatogram plot and a table of peak data. A "Signature" dialog box is open in the foreground, titled "Chromeleon 7 Review Signature", with fields for "User Name" (CmServiceAMS), "Signature Password", and "Comment".

No.	Peak Name	Retention Time (min)	Area (mAU*min)	Height (mAU)	Relative Area (%)	Relative Height (%)	Amount (mg)
1	Unaid	0.022	0.020	214.748	7.12	7.75	20.0000
2	Acetophenone	0.280	1.100	350.170	12.48	12.20	20.0000
3	Acetylphenone	0.293	1.200	320.291	14.21	14.20	20.0000
4	Propiophenone	0.291	1.011	322.219	12.17	10.52	20.0000
5	Butylphenone	0.2817	0.380	251.265	10.51	3.20	20.0000
6	Phenylphenone	0.280	0.200	251.215	6.52	7.20	20.0000
7	Chlorophenone	0.120	0.200	250.261	8.22	8.21	20.0000
8	Hexachlorophenone	0.145	0.210	220.265	7.22	10.51	20.0000
9	Hexachlorophenone	0.145	0.210	220.265	7.22	10.51	20.0000
10	Hexachlorophenone	0.145	0.210	220.265	7.22	10.51	20.0000

- Electronic report
  - Snapshot in time of sequence
  - Any changes tracked
  - Can be sent for review
- Electronic signatures
  - 3 Levels of signature Submit, Review, Approve
  - Applied to electronic report
  - Complete sequence protected by checksums
  - Controlled by privileges

# Record Management – Data Control

The screenshot displays three overlapping windows from the ThermoFisher Scientific software interface. The background window is titled "CmServiceAMS - RSLC Alkylphenone Linearity 2013-10-11 10-21-53" and features a "Submit" button highlighted with a red box. The middle window, titled "Enter Chromeleon User Name And Signature Password", shows the "Submit Signature" process with fields for "User Name" (CmServiceAMS), "Signature Password" (masked with asterisks), and a "Comment" field containing "Submitting sequence". The foreground window, titled "Submitting Results", lists the following items as submitted:

- Sequence Layouts**
  - 'SequenceLayout' submitted
- Sequence Definitions**
  - 'SequenceDefinition' submitted
- eWorkflows**
  - 'RSLC Alkylphenone Linearity' submitted
- View Settings**
  - 'RSLC Linearity' submitted
- Electronic Reports**
  - 'RSLC Alkylphenone Linearity 2013-10-11 10-21-53' submitted
- Sequences**
  - 'RSLC Alkylphenone Linearity 2013-10-11 10-21-53' submitted

A yellow text box at the bottom of the image states: "The sequence is signed. Modifications to the sequence are not possible."

# Record Management – Archive/Backup

- Chromeleon scheduler – Automatically archive/backup data using powerful injection queries
  - Transfer to another data vault – Direct access with full metadata
- Export to cmbx or other format (e.g. PDF, GAML, XLS, etc.)

Chromeleon Administration Console (nlams-cm02)

Scheduler is running. Last retrieval of service data: 23-Dec-13 14:43:52

Enabled	Task Name	Status
<input checked="" type="checkbox"/>	Archive Data older than one month	Waiting
<input checked="" type="checkbox"/>	Cleanup cached network sequences	Waiting

Chromeleon Administration Console (nlams-cm02)

Task is done. Next start: 23-Jan-14 14:26:24 Last retrieval of task data: 23-Dec-13 14:44:57

Name: Archive Data older than one month

Owner: Barbara van Cann

Description: Archive all data that is older than one month to the central archiving data vault.

Enabled

Specify additional settings that affect the behavior of the task:

If the task fails, restart every: 1 hour

Attempt restart up to: 3 times

Buttons: Terminate, Stop, Start, Delete, Discard changes, Save changes

- Introduction
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- Data integrity and compliance go hand-in-hand
  - Subject to elevated scrutiny by regulatory bodies
- Chromeleon CDS meets all of your data integrity needs:
  - Ensures completeness, consistency, and accuracy of data
    - ALCOA+
  - Comprehensive audit trails
    - Who, what, when and why of data
  - Maintains record authenticity
    - Contemporaneous collection
    - Automated long-term data retention with easy accessibility

- Introduction
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# Thank you for your attention!



## Any questions

**Do you have additional questions or do you want to talk to an expert from Thermo Fisher Scientific?**

Please send an E-Mail to [analyze.eu@thermofisher.com](mailto:analyze.eu@thermofisher.com) and we will get back to you.