Audit-Proof Your CMS

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Vaisala in Brief

- We serve customers in weather and industrial markets
- 80+ years of providing a comprehensive range of innovative observation and measurement products and services

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Vaisala - Life Science

Our Offering

Provides measurement instrumentation, continuous monitoring systems and validation systems for regulated or highly controlled life science environments.

Our Goal is to help customers

- Reduce their risk of lost or adulterated product
- Reduce their risk of failing to meet GxP regulations and/or guidelines

Audit-Proof Your CMS

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Goal: Audit-Proof your CMS

- Review of Audits and Regulations
- GxP Systems vs GxP Computerized Systems
- 5 basic GxP areas for focus when “Audit-proofing”

Basic Audit Conversation

- Auditor: “Show me how you perform task “X”.”
- You: “Let’s look at the SOP for task “X”.”
- Why: There are two basic things in GxP Audits
  - Written Procedures (What you said you would do)
  - Documented Results (Proof that you did it)

Regulations and Guidance

- FDA
- EMA
- ICH
- WHO
- USP
- ISPE
- PDA

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Regulations

- FDA - 21 CFR Part 211
  - Current Good Manufacturing Practice for Finished Pharmaceuticals
- FDA - 21 CFR Part 820
  - Quality System Regulation
- EMA – ICH Topic 7 (CPMP/ICH/4106/00)
  - GMP for APIs

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CMS Audit-Proofing Elements

- SOPs
- Training
- Calibration
- Validation
- Change Control

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- Same 3 Questions
  - Do I have a SOP?
  - Is the SOP adequate?
  - Did I follow the SOP?

Warning Letters… Environmental Control

- Gujurat, India – 2018
  - Drug Manufacturer (Oral care products)
    - "Your firm failed to provide equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature when appropriate for the manufacture, processing, packing, or holding of a drug product (21 CFR 211.46(b))."
  - **No Air Handling System**
  - **No control and monitoring of temperature and humidity**
  - **Temperatures in facility reach over 50C during hot weather months**

- New South Wales, Australia – 2013
  - Pharmaceutical Contract Packaging Facility
    - "Your firm failed to provide equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature when appropriate for the manufacture, processing, packing, or holding of a drug product (21 CFR 211.46(b))."
  - **No mechanism for control of humidity leading to brittle packaging**

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SOPs

FDA on SOPs

- 21 CFR 211.142 – Subpart H – Holding and Distribution

"Written procedures describing the warehousing of drug products shall be established and followed. They shall include… Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity."

EMA and ICH on SOPs

- EMA: ICH Topic Q7 – 5.4 Computerized Systems

  "Written procedures should be available for the operation and maintenance of computerized systems."

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SOP Evaluation Criteria

- SOP must…
  - Exist
  - Be adequate to the task
  - Copies available in work locations
  - Be maintained under document control
    - Version Control
    - Revision Dates
    - Approvals

- Authors preference:
  - Describe the process, not the specific interface actions.
  - Reference the User Guide for details.

Common SOP Topics for CMS

- Classic
  - Data Logger Locations and Sampling Rates*
  - Alarm Settings and Configuration*
  - Alarm Management and Response
  - Calibration Management
- Computerized
  - User Management and Access Review*
  - Password Management and Protection
- IT Backend
  - Backup and Recovery
  - Disaster Recovery
  - Change Control

(* = May be a specification doc)

Warning Letters… Written Procedures

- Wisconsin, USA – 2014
  - Pharmaceutical Contract Manufacturer
    - "Your firm failed to establish parameters for monitoring room temperature and humidity in your clean room." (Failure to adequately establish procedures to control environmental conditions, as required by 21 CFR 820.70(c))
  - **Temperature and Humidity Monitoring SOP lacked acceptance criteria.**

- Genova, Italy – 2013
  - Medical Device Manufacturer
    - "Failure to establish and maintain procedures to adequately control environmental conditions that could reasonably be expected to have an adverse effect on product quality. Environmental control systems shall be periodically inspected to verify that the system, including necessary equipment, is adequate and functioning properly. These activities shall be documented and reviewed, as required by 21 CFR 820.70(c)."
  - **Temperature and Humidity Monitoring SOP did not specify how to document or respond to OOS events.**

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TRAINING

FDA on Training

- 21 CFR 820.25(b) – Training

"Each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities. Training shall be documented."

EMA and ICH on Training

- EMA: ICH Topic Q7 – 3.1 Personnel Qualifications
  - *There should be… personnel qualified by appropriate education, training and/or experience to… manufacture… APIs.*
  - *The responsibilities of all personnel… should be specified in writing.*
  - *Training should be regularly conducted… and should cover… the particular operations that the employee performs and GMP as it relates to the employee's functions.*
  - *Records of training should be maintained.*

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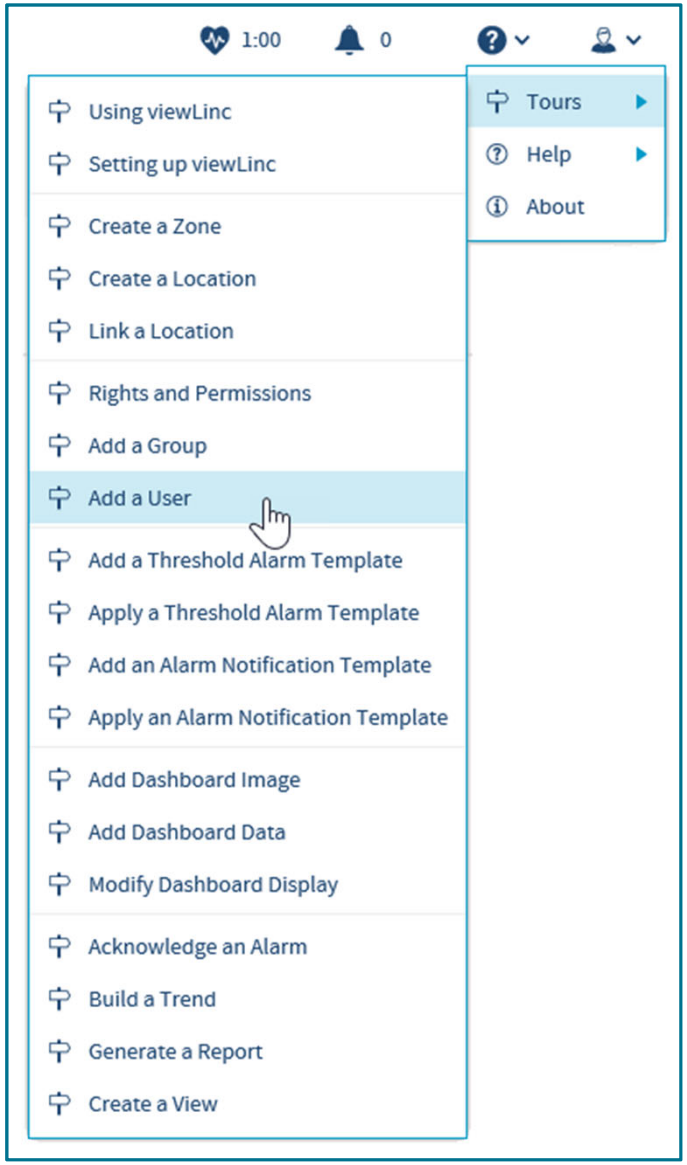
Best Practices for Training

- Written procedure or policy, including…
  - Train employees to SOPs in areas of responsibility.
  - Repeat training for…
    - New SOP revisions.
    - New employees.
  - Keep written records of training.
  - Keep employee CV on file.

viewLinc and Training

- Introducing “viewLinc Tours”
  - An on-board training tool.
    - Learn while doing.
    - Task completed during training.
  - Tours for every routine task
  - Integrate SOPs and Tours
    - Simple SOPs
    - Increased Compliance



Warning Letters… Training

- Seoul, South Korea – 2018
  - Medical Device Manufacturer
    - "Failure to establish adequate procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities, as required by 21 CFR 820.25(b)."
  - **No training records exist for multiple SOPs.**

- Bavaria, Germany – 2015
  - Prescription Drug Manufacturer
    - Failure "…to ensure that each person engaged in the manufacture… of a drug product has the education, training, and experience… to perform his or her assigned functions… (21 CFR 211.25(a))."
  - **Training provided in English only to employees that don't speak English.**
  - **Failed training forms found in trash, official records show passing results.**

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CALIBRATION

FDA on Calibration

- 21 CFR 211.68 – Automated, Mechanical, and Electronic Equipment

"Automatic, mechanical, or electronic equipment... used in the manufacture, processing, packing, and holding of a drug product… shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained."

EMA and ICH on Calibration

- EMA: ICH Topic Q7 – 5.3 Calibration
  - "[Equipment] that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule."
  - "Equipment calibrations should be performed using standards traceable to certified standards, if existing."
  - Records of these calibrations should be maintained."

EMA and ICH on Calibration (cont'd)

- EMA: ICH Topic Q7 – 5.3 Calibration
  - "The current calibration status of critical equipment should be known and verifiable."
  - "Instruments that do not meet calibration criteria should not be used."
  - "Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s)…"

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Best Practices for Calibration

- Written Calibration Program
- Written Calibration Procedures
  - Traceable standards
- Regular Calibration Intervals
  - Labeled Instruments
- Written Calibration Records
- Quarantine failed devices
  - Investigate failures

viewLinc and Calibration

- Data Loggers store calibration Dates
  - Dates included in Reports
  - Calibration Reminder Warnings
- Smart Probes
  - Leave data logger in service, and swap probe only
- Alarm Pause
  - Prevent false alarms during in situ calibration
  - Alarming automatically restarts

Warning Letters… Calibration

- California, USA – 2014
  - Nutritional Supplements Manufacturer
    - "Your firm did not calibrate instruments or controls used in manufacturing or testing a component or dietary supplement to ensure the accuracy and precision of the instruments or controls as required by 21 CFR 111.27(b)."
  - **Failure to calibrate thermometer for over 3 years.**

- New York, USA – 2019
  - Contract Medical Device Manufacturer
    - "Failure to ensure equipment used for manufacturing, inspection and/or testing is routinely calibrated as required by 21 CFR 820.72(a)."
  - **Manufacturing equipment not calibrated according to a schedule.**
  - **Some manufacturing equipment was never calibrated.**
  - **Calibration SOP has no revision date.**

Top 7 Reasons: Calibration Warning Letters

- Calibration procedures are inadequate
- Calibration is not performed
- Calibration procedures are not documented or followed
- Deviations not reported
- No formal procedure for deviation management
- Calibration records not maintained
- Calibrations being missed

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VALIDATION

FDA on Validation

- 21 CFR 820.70 - Production and Process Controls

  "When computers… are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use… These validation activities and results shall be documented."

EMA and ICH on Validation

- EMA: ICH Topic Q7 – 5.4 Computerized Systems
  - "GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application."
  - "Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks."

Best Practices for Validation

- Validate your monitoring system
  - This is much better than having no validation in place.
  - Approve (before) and review (after) the execution.
  - Store the document safely
- Include CMS in Validation Master Plan
  - Get validation department involved early
  - Create User Requirements BEFORE selecting system
- Incorporate a risk-based approach
  - Test all high-risk functions
- Address Part 11/ Annex 11 concerns in validation process
  - Electronic Records Management
  - Data Integrity

viewLinc and Validation

- Full IQOQ for viewLinc software
  - The vendor protocol is a good place to start.

- GxP System Documentation
  - User Requirements
  - Functional Specification
  - Risk Assessment
  - Traceability Matrix

Warning Letters… Validation

- Seoul, South Korea – 2013
  - Medical Device Manufacturer
    - "Failure to validate computer software for its intended use according to an established protocol… as required by 21 CFR 820.70(i)."
  - **Failure to perform software validation.**
  - **No user requirements.**

- Seoul, South Korea – 2018
  - Medical Device Manufacturer
    - "Failure to validate computer software for its intended use according to an established protocol… as required by 21 CFR 820.70(i)."
  - **Technician could click both Pass and Fail of the same test without error.**

Warning Letters… Part 11 and Data Integrity

- Tel Aviv, Israel – 2016
  - Pharmaceutical Manufacturer
    - "Your firm failed to exercise appropriate controls over computer… systems to assure that only authorized personnel institute changes in… records. (21 CFR 211.68(b))"
  - **Employees could delete data.**
  - **No audit trail review.**
  - **Response criticized for "random review of audit trails"**

- Mumbai, India – 2014
  - API Manufacturer
    - "Your firm failed to exercise appropriate controls over computer… systems to assure that only authorized personnel institute changes in… records. (21 CFR 211.68(b))"
  - **Audit trail disabled.**
  - **Operators shared usernames and passwords.**
  - **No security controls to prevent unauthorized access to Operating System.**
  - **No SOP for backup and protection of data.**

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CHANGE CONTROL

IT Professionals on Change Control

- From Cisco's "Change Management: Best Practices"

"The objective of the change management process is to minimize service downtime by ensuring that requests for changes are recorded and then evaluated, authorized, prioritized, planned, tested, implemented, documented and reviewed in a controlled and consistent manner."

FDA on Change Control

- 21 CFR 820.70 - Production and Process Controls

"Each manufacturer shall establish… procedures for changes to a… process, or procedure. Such changes shall be… validated… before implementation… Changes shall be approved..."

EMA on Change Management

- EMA: Annex 11: Computerised Systems
  - Change and Configuration Management

"Any changes to a computerised system including system configurations should only be made in a controlled manner in accordance with a defined procedure."

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ICH Change Control Guidelines

- ICH Q10 3.2.3 – Change Management System
  - (a) – Quality risk management should be utilized to evaluate proposed changes.
  - (c) – Proposed changes should be evaluated by expert teams... to ensure a change is technically justified
  - (d) - After implementation, an evaluation of the change should be undertaken to confirm the change objectives were achieved and that there was no deleterious impact on product quality.

Best Practices for Change Control

1. Have a written process

2. Follow the process
   a) Describe
   b) Pre-Approve
   c) Execute
   d) Test
   e) Review

3. Document the process

Warning Letters… Change Control

- Tianjin, China – 2014
  - API Manufacturer
    - "Your firm failed to conduct a change control investigation or document the significant changes in [production] systems as required by your change control procedure…"
  - **Employees did not comply with Change Control Procedure.**
  - **Employees were not trained to Change Control Procedure.**
  - **System drawings were not current.**

- California, USA – 2011
  - Pharmaceutical Manufacturer
    - Your firm failed to ensure that… electronic equipment… including computers or related systems, will perform a function satisfactorily [per] 21 CFR 211.68(a)".
  - **Over 25 changes to custom system with no rationale or revalidation.**

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Leverage your resources…

- SOPs → QA Doc Mgt.
- Training → Training Mgt.
- Calibration → Calibration Mgt.
- Validation → Validation Dept.
- Change Control → IT Experts

Build Quality…

"Quality should be built into the product, and testing alone cannot be relied on to ensure product quality."

FDA Guidance for Industry: Quality Systems Approach to Pharmaceutical cGMP Regulations, 2006

Review: Audit-Proof your CMS

- Review of Audits and Regulations
- GxP Systems vs GxP Computerized Systems
- 5 basic GxP areas for focus when “Audit-proofing”

Question Break

The VAISALA blog!

- Updated every Wednesday
- Technical information on measurement
- Regulatory & Guidance updates
- Event information from associations like ISPE, MSC, PDA
- And more!

Bookmark: www.vaisala.com/lifescience-blog

Thanks for Attending!

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