

dcvmn
Developing Countries Vaccine
Manufacturers Network

Regional workshop: Cost-effective Purification of Vaccines,
Data Integrity Systems and CTDs



Dr. Sandra Olga Rumiano

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Developing Countries Vaccine
Manufacturers Network

Data Integrity session
Hosted by DCVMN
Day 2

Dr. Sandra O. Rumiano
June 18th and 19th 2018

Inspectors expectations on industry from different authorities: FDA, ANVISA, MHRA, WHO

- The main regulatory expectation for data integrity is to comply with the requirement of ALCOA (Attributable, Legible, Contemporaneous, Original, Accurate) principles for API and FP. Including:
 - General Documentation (SMF, Quality Manual, Policies, VMP, others)
 - Production documentation (BR) and records (ie differential pressure sheet, T/RH%, cleanign sheets, etc).
 - Quality control documentation (analyst logbooks) and réconds (Stability Protocol, raw data and Report, equipments logs, T/RH% sheets, etc)
 - Equipments and sistems Audit trail

Inspectors expectations on industry from different authorities: FDA, ANVISA, MHRA, WHO

- The main regulatory expectation for data integrity is to comply with the requirement of ALCOA (Attributable, Legible, Contemporaneous, Original, Accurate) principles for API and FP. Including:
 - Process equipment (computerized system / no computerized): logs, calibrations status, qualification status & verification, maintenance program & records, etc.
 - Computerised Systems: SOPs, challenges, CSV & continuous verification
 - Archiving and archivist role
 - Data entry role

Inspectors expectations on industry from different authorities: FDA, ANVISA, MHRA, WHO

- The main regulatory expectation for data integrity is to comply with the requirement of ALCOA (Attributable, Legible, Contemporaneous, Original, Accurate) principles for API and FP. Including:
 - ERP like SAP: secure measures
 - Job description and induction as well as continuous training including GDocP&DI
 - Contracts & Quality Agreements
 - Clear role of parts
 - Cover each step contracted by ALCOA

Inspectors expectations on industry from different authorities: FDA, ANVISA, MHRA, WHO

- The main regulatory expectation for data integrity is to comply with the requirement of ALCOA (Attributable, Legible, Contemporaneous, Original, Accurate) principles for API and FP. Including:
 - OOS , OOT, deviation management, change control, PPQR documents and CAPA follow up
 - Inspection/Internal/External audits & CAPA follow up
 - Storage documents
 - Dispatch and Distribution documents

Inspectors expectations on industry from different authorities: FDA, ANVISA, MHRA, WHO

- Paper requirements = electronic requirements
 - Requirements for record retention and review do not differ by data format.
 - Paper-based and electronic data record-keeping systems are subject to the same requirements.
- Relationships between data and their metadata should be preserved in a secure and traceable manner (ie analyst log books, BR RM weights, BR conciliation, etc.)

Typical documentation failures and how to avoid them key learning points

- Incomplete documentation
 - Complaint all the time without make a phone call or a meeting
 - Try to solve the problem and not the root cause
- Documents are completed late
- Lack of Documentation traceability challenges
- Lack of CAPA Plans follow up

Key learning points

- Data Integrity and its Governance is the Focus
- Policies, Procedures, and Training:
 - Data integrity training will be given as first time and on an annual basis for all employees.
 - The training must include organizational mission, the critical need for honesty, and full disclosure in all analytical reporting, plus how and when to report data integrity issues and record keeping.
 - Training will include discussion of all data integrity SOPs and training documentation including how to document analytical records.
 - Employees must understand that failure to follow the laboratory data and or manufacturing, storage, distribution data and procedures will result in a detailed investigation that could lead to very serious consequences for the Health of the Public

Key learning points

- Data Integrity and its Governance is the Focus
- Policies, Procedures, and Training:
 - A copy of all training materials will be given to each trainee and kept, including signature attendance sheets
 - Evaluation to demonstrate understanding
 - Senior managers actively support and implement the data integrity procedures.
 - Specific examples of breaches of unethical behavior should be discussed
(improper data manipulations, no calibrated and use, inappropriate changes in
 - Data integrity training requires emphasis on the importance of proper recording of data with examples of both poor and acceptable records.
 - **Information and commitment about ethics should be available and agree by employees.**

Detection of poor documentation practices and falsification

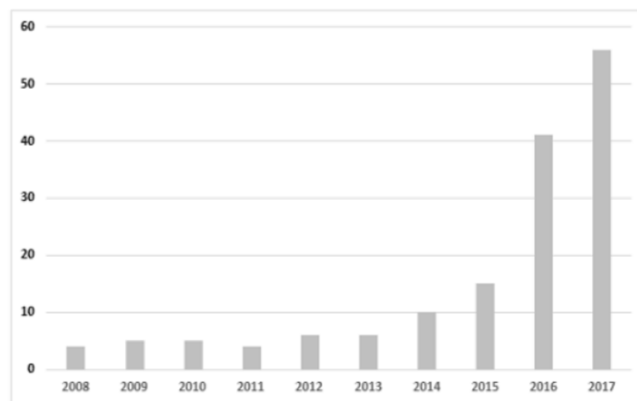


Figure 2: Data integrity associated warning letters, CY2008-CY2017

Source:

29/5/2018



PHARMACEUTICAL
ONLINE

Guest Column | May 18, 2018

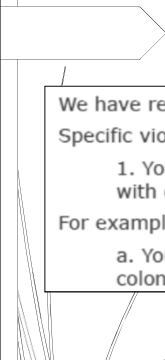
An Analysis Of 2017 FDA Warning Letters On Data Integrity

An Analysis Of 2017 FDA Warning Letters On Data Integrity

By Barbara Unger, Unger Consulting Inc.



More than statistics....



We have reviewed your firm's response of February 10, 2011, and note that it lacks sufficient corrective actions. Specific violations observed during the inspection include, but are not limited, to the following:

1. Your firm's laboratory records fail to include complete data derived from all tests necessary to assure compliance with established specifications and standards [21 C.F.R. § 211.194].

For example,

- a. Your microbiologists reported the MA 5 and MA 6 microbiological plates as "nil" while each plate contained one (1) colony forming unit (CFU).

On January 21, 2011, the FDA investigator observed the microbiological plates, MA 5 and MA 6, from air sampling locations in the Class 100/Grade A laminar air flow cabinet in the Microbiology Lab. Each microbiological plate contained one (1) CFU/m3. Your microbiologists reported these microbiological plates as "nil" on your form FM/QC/252-9 Quality Control Department Record of Environmental Monitoring of Microbiology Laboratory. However, the action limit for these sample locations is **(b)(4)** CFU/m3 which requires an investigation per your procedure SOP/QC/049 entitled Environment Monitoring of Aseptic Area by Settle Plate, Air Sampling, Surface Sampling (RODAC Plate) and Personnel Hygiene for Viable Count. The results as originally reported on your form FM/QC/252-9 would not have prompted an investigation.

- b. The microbiological growth found on settle plate MS 4 was incorrectly identified and reported as a typical microorganism when compared against your firm's library/photographs of typical environmental flora.

Your microbiologists identified the growth on the MS 4 plate as typical flora. However, the FDA investigator found that when compared with your normal environmental flora, the growth should have been reported as atypical since the microorganism identified is not included in firm's library/photographs of typical environmental flora. Your written procedure SOP QC/049 requires further identification of microbial growth not included in your firm's library/photographs. The results originally reported on your form FM/QC/252-9 (typical flora) would not have prompted further identification.

Your response recognized that the microbiologists should have classified the MS 4 microorganism as atypical. Moreover, your response indicated that an investigation was performed and microbiologists were retrained. You stated that as part of your corrective actions two microbiologists will observe counts for three months to "rule out any possibility of erroneous reporting." However, during the inspection, the FDA investigator observed two microbiologists reading plates and recording data. Therefore, your corrective action plan does not adequately address the observation, nor does it appear to improve or current practices for reading plates and recording data. Additionally, the revised form used to document the microbiologist observation lacks appropriate identification of the microbiologist performing the task at the time of the final reading of the plates.

You are responsible for the accuracy and integrity of the data generated by your firm. We are concerned that trained microbiologists employed by your firm were unable to accurately identify microbial growth on environmental monitoring plates. Additionally, there is no assurance that such errors have not occurred previously (during the manufacture of exhibit batches for application products pending with FDA). Provide a more comprehensive corrective action plan to ensure the integrity of all data used to assess the quality and purity of all drugs manufactured at your facility, including any registration lots.

Accurate and reliable microbiological data is essential to support the aseptic processing operations used during the manufacturing of sterile finished drug products intended for distribution in the United States. Your response includes retraining documentation related to identifying environmental isolates as typical/atypical and observation of microbial growth, as well as retraining on SOP QC/049. According to information provided to the FDA investigators during the inspection, the Microbiology Laboratory is staffed by (b)(4) microbiologists. The training attendance sheets in your response do not include the same individuals. For example, 10 QC personnel attended the training on observation and counting of colonies on environmental monitoring plates held on January 22, 2011; and, only 8 QC personnel attended the training on identifying typical/atypical environmental isolates during environmental monitoring plate observation. Explain this discrepancy and provide documentation confirming that all employees have been retrained. Additionally, provide documentation of specific training offered to all employees regarding the importance of following CGMP, and ensuring that they accurately report all required tests.

2. Your firm has not established or followed appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. § 211.113(b)].

For example,

a. Your firm's environmental monitoring is inadequate in relation to personnel monitoring.

Our investigators found that gowns worn by operators working in the aseptic processing areas are only monitored (b)(4) per week. Additionally, gloves are only monitored at the (b)(4) the shift. We are concerned with the fact that operators performing critical operations may not be adequately monitored. Therefore, there is no assurance that your environmental monitoring program is capable of detecting all microbiological contaminants.

Since personnel can significantly affect the quality of the environment, a robust personnel monitoring program should be in place in order to be compliant with CGMPs. Your response indicates that SOP/QC/049 was revised to require additional monitoring of gloves after (b)(4) for personnel involved in aseptic connections on filling line and filtration activities apart from regular monitoring at the (b)(4) of the shift. It is your responsibility to ensure that all personnel involved in aseptic processing are properly monitored on a daily basis, or in association with each lot. We acknowledge that SOP/QC/049 has now been revised to require sampling of gowns per (b)(4)/per (b)(4).

1) You failed to assure that appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, are established and followed. Such procedures include validation of all aseptic and sterilization processes [21 CFR 211.113(b)]. Specifically, deviation #200217121 was initiated March 5, 2012, to investigate out of trend (OOT) results for endotoxin. The average endotoxin in the first 20 seasonal (b)(4) monovalent lots for 2012 was higher than the first 20 in 2010, and 2011. The investigation concluded that the endotoxin results have been atypical since May 2011.

Additionally, significant deviations in the manufacture of your intermediates were observed during the inspection. These deviations violate Section 501(a)(2)(B) of the FD&C Act and the requirements of your BLA approved under Section 351(a) of the PHS Act. Specific areas of concern include, but are not limited to:

2) Controls for the purified water system at your facility are inadequate to prevent bioburden and endotoxin excursions. For example:

- a. The 2012 Annual Product Quality Review report for water indicates that there were many bioburden excursions in purified water system (b)(4)(Loop (b)(4)). Water from Loop (b)(4) is used in part to humidify air in (b)(4). Different types of bacteria were found, but in the majority of cases, the microorganisms found were *Ralstonia pickettii* and *Achromobacter spp.*
- b. Deviation #200217554, initiated on March 7, 2012, indicates that a water-borne organism, *Achromobacter xylosoxidans*, found in water from one of the farms, and in water from one of the hatcheries, was also isolated from the purified water system in your facility.
- c. The 2013 Annual Product Quality Review report for water concludes that four alert limits and one action limit were reached for water system (b)(4) (Loop (b)(4)). Water from Loop (b)(4) is used in part for equipment washing. Organisms isolated from these five excursions included *Ralstonia pickettii* and *Achromobacter xylosoxidans*. *Achromobacter xylosoxidans* and other water borne gram negative bacteria have been implicated in product contamination issues at your facility as far back as 2011.
- d. There is no set schedule for disinfection of your water system. The system is only disinfected on (b)(4). The system was disinfected twice in 2011, five times in 2012, four times in 2013, and once in 2014 to date. In addition, the water system is circulated at (b)(4) temperature and is cleaned with (b)(4). No (b)(4) is used in the system.

FAILURE INVESTIGATIONS

5) Your investigation into the repeated bioburden excursions associated with (b)(4) is inadequate. You used a (b)(4) approach (testing 3 of the (b)(4)) to investigate the (b)(4), even though (b)(4) was most often implicated. (b)(4) was not always tested. For example:

- a. In April 2013, contamination of (b)(4) was identified as the root cause for the 80% mortality rate of (b)(4) eggs. The eggs were found contaminated with *Achromobacter xylosoxidans*. The investigation in June, 2013, included taking swab samples from the (b)(4). Swabs taken from (b)(4) were tested for bioburden but the swab sample taken of (b)(4) was not tested for bioburden, even though it was the (b)(4) implicated in the contamination event.
- b. A new cleaning validation study was approved and implemented in January 2014. The study included (b)(4) steps. The study did not include (b)(4).
- c. On March 31, 2014, a new (b)(4) cleaning cycle was validated and implemented for the (b)(4). The study did not include (b)(4).

1. Failure to prevent unauthorized access or changes to data, and failure to provide adequate controls to prevent omission of data.

Our inspection found your laboratory systems lacked controls to prevent deletion of and alterations to electronic raw data.

- a. Our review of audit trail data revealed that your analysts manipulated the date/time settings on your high performance liquid chromatography (HPLC) systems. During the inspection your analysts admitted to setting the clock back and repeating analyses for undocumented reasons. Initial sample results were overwritten or deleted, and unavailable for our investigators' review. Your firm reported only the passing results from repeat analyses. When test results are overwritten, the quality unit is presented with incomplete and inaccurate information about the quality of the drugs produced by your firm.
- b. Your quality control analysts used a shared login account to access HPLC systems. This shared account allowed analysts, without traceability, to change the date/time settings of the computer, to modify file names, and to delete original HPLC data.
- c. Seven out of (b)(4) of your firm's HPLC systems used for API testing had the audit trail feature disabled, although all (b)(4) had audit trail functionality.

Batch record review is also rather difficult for the [REDACTED] The reason is obvious: they "failed to prepare batch production and control records with complete information relating to the production and control". At least they were honest and told the inspector that "there was not a batch record for each batch".

3. Failure to have appropriate documentation and record controls.

a. Critical information necessary to assure the traceability of all the raw materials used during the production of (b)(4) USP was not maintained. Our inspection found that your firm placed correction tape over multiple entries of raw material batch numbers in a logbook used to track crude (b)(4)(raw material) used for the manufacture of (b)(4) USP. In addition, you used correction fluid on a recurring basis to make corrections in a logbook used to record various details of (b)(4) within the (b)(4) USP manufacturing process. Corrections to entries should be dated and signed, and the original entry must remain legible for review.

In addition, your current SOP SGL-SOP-GEN-001 "Correct Way of Making Monitoring Records," prohibits the use of white ink for corrections of *any written matter*; however, operator training records did not show training on this procedure.

It is your responsibility to ensure that all applicable operators are trained on your procedures. Please provide assurance that this procedure is fully implemented and provide a corrective action plan that prevents the recurrence of this deficiency.

New England Compounding: Meningitis Outbreak 2012

Pharmacy technicians instructed to prioritize production over cleaning and disinfecting

Pharmacy technicians instructed to falsify cleaning records

Neglected to investigate contamination found in the clean rooms

64 reported deaths, >800 patients sickened

President sentenced to 9 years in prison

Other employees charged with multiple criminal acts

Takata: Auto Airbags 2015

- Potential danger of spraying shrapnel caused by defective air bag inflators when the air bag goes off
- Takata engineers removed some test results to artificially reduce variability in air-bag inflator performance
- "Takata provided inaccurate, incomplete and misleading information to regulators for nearly a decade," said NHTSA spokesman Bryan Thomas. "Had they told the truth, Takata could have prevented this from becoming a global crisis."

15 deaths, 100 injuries
100 million vehicles worldwide, ~33 million in US
Defective airbags still in cars

Toyota
example

Peanut Corporation of America: Salmonella Outbreak 2008-09

- In some cases, company officials falsified lab results, stating peanut products were safe to eat when tests showed otherwise, or when products had never been tested at all, according to court papers. - The Wall Street Journal
- The company shipped product with falsified Certificates of Analysis (COA), which attested to the purity of contaminated lots
- CEO wrote in a March 2007 email to a plant manager about contaminated products: "**Just ship it.** I cannot afford to lose another customer."

9 reported deaths, >700 consumers sickened
CEO sentenced to 28 years in prison;
others sent to prison including Plant Quality Manager
Plant closed & company liquidated



Audit Trail Review



What are ‘computer systems’ and “control” in WHO GDocP&DI?

computerized system. A computerized system collectively controls the performance of one or more automated processes and/or functions. It includes computer hardware, software, peripheral devices, networks and documentation, e.g. manuals and standard operating procedures, as well as the personnel interfacing with the hardware and software, e.g. users and information technology support personnel.

control strategy. A planned set of controls, derived from current protocol, test article or product and process understanding, which assures protocol compliance, process performance, product quality and data reliability, as applicable. The controls should include appropriate parameters and quality attributes related to study subjects, test systems, product materials and components, technologies and equipment, facilities, operating conditions, specifications and the associated methods and frequency of monitoring and control.

What is an 'audit trail'?

Secure, computer-generated, time-stamped electronic record that allows for reconstruction of events relating to the creation, modification, or deletion of an electronic record

Chronology: who, what, when, and sometimes why of a record

CGMP-compliant record-keeping practices prevent data from being lost or adulterated /modified

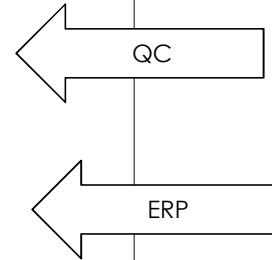
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As per WHO GDocP&DI guideline

- For example, in a paper record, an audit trail of a change would be documented via a single-line cross-out that allows the original entry to remain legible and documents the initials of the person making the change, the date of the change and the reason for the change, as required to substantiate and justify the change. In electronic records, secure, computer-generated, time-stamped audit trails should allow for reconstruction of the course of events relating to the creation, modification and deletion of electronic data. Computer-generated audit trails should retain the original entry and document the user identification, the time/date stamp of the action, as well as the reason for the change, as required to substantiate and justify the action. Computer-generated audit trails may include discrete event logs, history files, database queries or reports or other mechanisms that display events related to the computerized system, specific electronic records or specific data contained within the record

Audit trails Can find

- Overwriting
- Aborting runs
- Testing into compliance
- Deleting
- Backdating
- Altering data



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How often should audit trails be reviewed?

For audit trails that capture changes to *critical data*, recommends review of each record before final approval of the record.

Audit trails subject to regular review should include changes to:

- history of finished product test results
- sample run sequences
- sample identification
- critical process parameters
- Access protection
- Internal audits

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How often should audit trails be reviewed?

- FDA recommends routine scheduled audit trail review based on the complexity of the system and its intended use.

21

1. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data.

Laboratory equipment used to generate analytical data for batch release purposes by your quality unit lacked restricted access. For example, the high-performance chromatography (HPLC) and gas chromatography systems each had a single username with administrator rights. All users could delete or modify files, and there was no mechanism to trace individuals who may have created, modified, or deleted data generated by computerized systems.

In your response to a previous FDA inspection conducted March 30 to April 3, 2015, you committed to:

- enabling the audit trail function on laboratory electronic instruments;
- assigning unique user names and passwords for each staff member; and
- authorizing (b)(4) levels of accessibility to prevent electronic data from being deleted, removed, transferred, renamed or altered.

In the October 2017 inspection, our investigator observed that you had not implemented any of these promised corrective actions.

2. Failure to maintain complete data derived from all laboratory tests conducted to ensure your API and intermediates comply with established specifications and standards.

Your firm performed HPLC assay testing for (b)(4) API release to the United States, along with stability and intermediate testing, on your Waters HPLC system between September 25, 2011, and May 5, 2017. Official quality control data packages presented to the quality unit for batch disposition decisions reported the results of testing performed during this timeframe on this equipment. During our inspection, when we sought to reconcile assay results reported in the quality control data package for a released batch with the underlying electronic data, you responded that you could not provide the electronic data from laboratory analyses on this equipment for the above period of several years. You explained that the electronic data in question had been deleted by accident and was no longer available.

In your response, you stated that the electronic data had been downloaded to a "mobile hard disk for backup" and that you would be able to recover the data after you have upgraded your HPLC software. However, you did not include evidence to support recovery of deleted electronic data or demonstrate how you will prevent such deletions from recurring in the future.

4. Failure of your quality unit to review and approve all appropriate quality-related documents.


Your quality unit approved the certificate of analysis (COA) for release of an API batch to your customer before testing was complete and available for review.

During the inspection, our investigator reviewed the COA for (b)(4) API batch (b)(4). Your quality unit reviewed and approved this COA on May 29, 2015. However, the test for related substances on this batch was not performed until May 30, 2015. During the inspection, your quality control manager explained that this specific COA had been released early to the quality unit because it was urgent and needed to be provided to your customer.

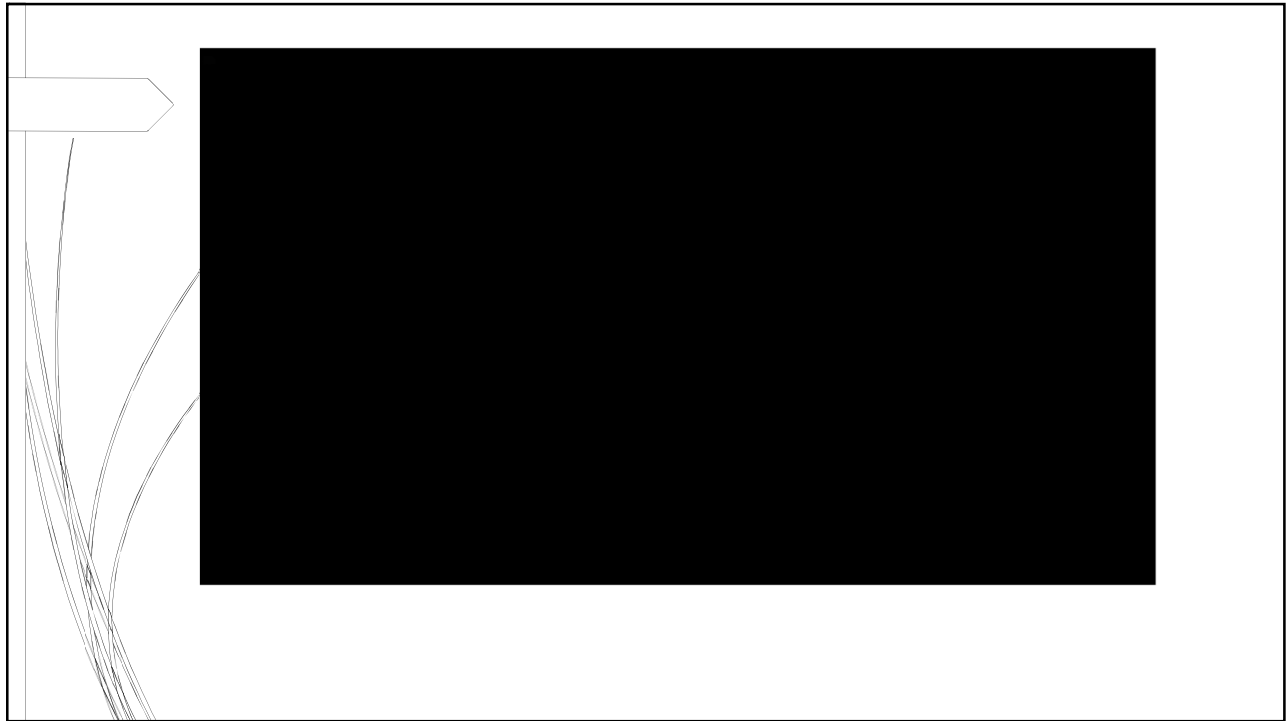


Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We strongly recommend that you retain a qualified consultant to assist in your remediation.




Log File Review

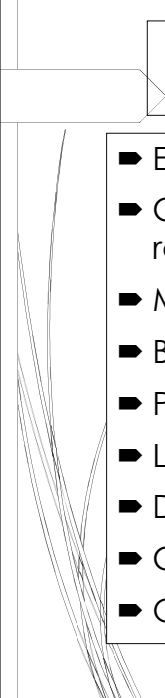


Note: dogs and cats are friendly and we don't have pest control policies against them at this Company



- 
- Batch record review is typically a verification step that confirms the acceptability of the manufacturing and packaging processes. If, however, the guarantee of efficacy, safety and quality of the product
 - Because the review process is so common, its importance may be overlooked beyond the regulatory requirement found in the current good manufacturing practices regulation.
 - Proper controls not only during internal audits but also after information from investigation of corrections , deviations, complaints, that can lead to both corrective and preventive action—even process improvement, should be in place

CGMP Key control records

- 
- Equipment cleaning and use log
 - Component, drug product container, closure, and labeling records
 - Master production and control records
 - Batch production and control records
 - Production record review
 - Laboratory records
 - Distribution records
 - Complaint files.
 - Others

BR review: at least but not only

- Dates; times; signatures
- Identity of individual major equipment and lines used
- Specific identification of each batch of component or in-process material used
- Weights and measures of components used in the course of processing
- In-process and laboratory control results
- Inspection of the packaging and labeling area before and after use
- A statement of the actual yield and a statement of the percentage of theoretical yield at each step of processing
- Complete labeling and packaging control records including materials conciliation
- Description of drug product containers and closures
- Any sampling performed
- Identification of the persons performing and directly supervising or checking each significant step in the operation
- Any investigation or observations made

Log maintenance: at least but not only

- Preventive maintenance Plan (PMP)
- Sheets in accordance to previous one
- SOPs for performing maintenance
- Deviations on maintenance not done
- Follow up of PMP
- Internal Audit challenge example

Log analyst : at least but not only

The analytical worksheet is an internal document to be used by the analyst for recording information about the sample, the test procedure, calculations and the results of testing. It is to be complemented by the raw data obtained in the analysis.

Numbered and review/revised with analyst

the registration from sample till final result: data traceability

- page numbering, including the total number of pages (and including annexes);, date of the test request; the name and signature of the analyst;
- Product, dosage, lot number, a description of the sample received;
- references to the specifications including the limits and analytical technique;
- the identification of the test equipment used and its status control
- the identification number of any reference substance used
- the identification of reagents and solvents employed;
- the results obtained and the interpretation of the results and the final conclusions
- approved and signed by the supervisor; and any further comments, for example, for internal information or any deviation from the prescribed procedure,
- tests and the date on which the results were received and All values obtained from each test, including blank results, should immediately be entered on the analytical worksheet and all graphical data, including instruments records
- The completed analytical worksheet should be signed by the responsible analyst/s
- The analytical worksheet should be kept safely together with any attachments, including calculations and recordings of instrumental analyses.

Data-processing equipment: at least but not only

- For computers, automated tests or calibration equipment, and the collection, processing, recording, reporting, storage or retrieval of test and/or calibration data, the laboratory should ensure that:
 - computer software developed by the user is documented in sufficient detail and appropriately validated or verified as being suitable for use;
 - procedures are established and implemented for protecting the integrity of data. Such procedures should include, but are not limited to, measures to ensure the integrity and confidentiality of data entry or collection and the storage, transmission and processing of data. In particular, electronic data should be protected from unauthorized access and an audit trail of any amendments should be maintained;
 - computers and automated equipment are maintained so as to function properly and are provided with the environmental and operating conditions necessary to ensure the integrity of test and calibration data;
 - procedures are established and implemented for making, documenting and controlling changes to information stored in computerized systems; and
 - Backed-up data and disaster recovery procedures



Log equipments: at least but not only

- Calibration status
- Qualification status
- The famous: out of used
 - When
 - Why
 - How long
 - Substitution is available
 - How work is done?



How to establish a compliant and under control process

- Major data and documentation problems may be categorized as data recording and storage, data responsibility and verification, and miscellaneous documentation practices.
- Actions to be implemented:
 - Details in documentation and policies and practices addressing the goal of staff understanding
 - Training on data and documentation practices based on own examples.
 - Senior management support of activities to address data and documentation problems is necessary for successful improvement of substandard practices.
 - Compliance personnel must continually be aware of the potential for documentation problems when original data are not routinely reviewed.
 - Controlling the issuance of blank paper templates for data recording of GXP activities so that all printed forms can be reconciled and accounted for

Actions to be implemented:

- Restricting user access rights to automated systems to prevent (or audit trail) data amendments;
- Ensuring automated data capture or printers are attached and connected to equipment, such as balances, to ensure independent and timely recording of the data;
- Ensuring ease of access to locations of sampling points (e.g. sampling points for water systems) to allow easy and efficient performance of sampling by the operators and therefore minimizing the temptation to take shortcuts or falsify samples;
- Restricting the ability to change any clock used for recording timed events, for example, system clocks in electronic systems and process instrumentation.
- Ensuring controlled forms used for recording GXP data (e.g. paper batch records, paper case report forms and laboratory worksheets) are accessible at the locations where an activity is taking place, at the time that the activity is taking place, so that ad hoc data recording and later transcription is not necessary



Actions to be implemented:

- Maintenance of record-keeping systems: owner responsibilities and back up
- Tracking and trending of invalid and aberrant data : Internal audits based on QRM principles and FPQR
- Systemic review of audit trails
- Contracts and Quality Agreements for third parties ie, archive companies follow up and auditing on compliance: is fire incidents are considering??
- To be trustful: GdocP&DI is culture and habit, not only Guidelines to be accomplished



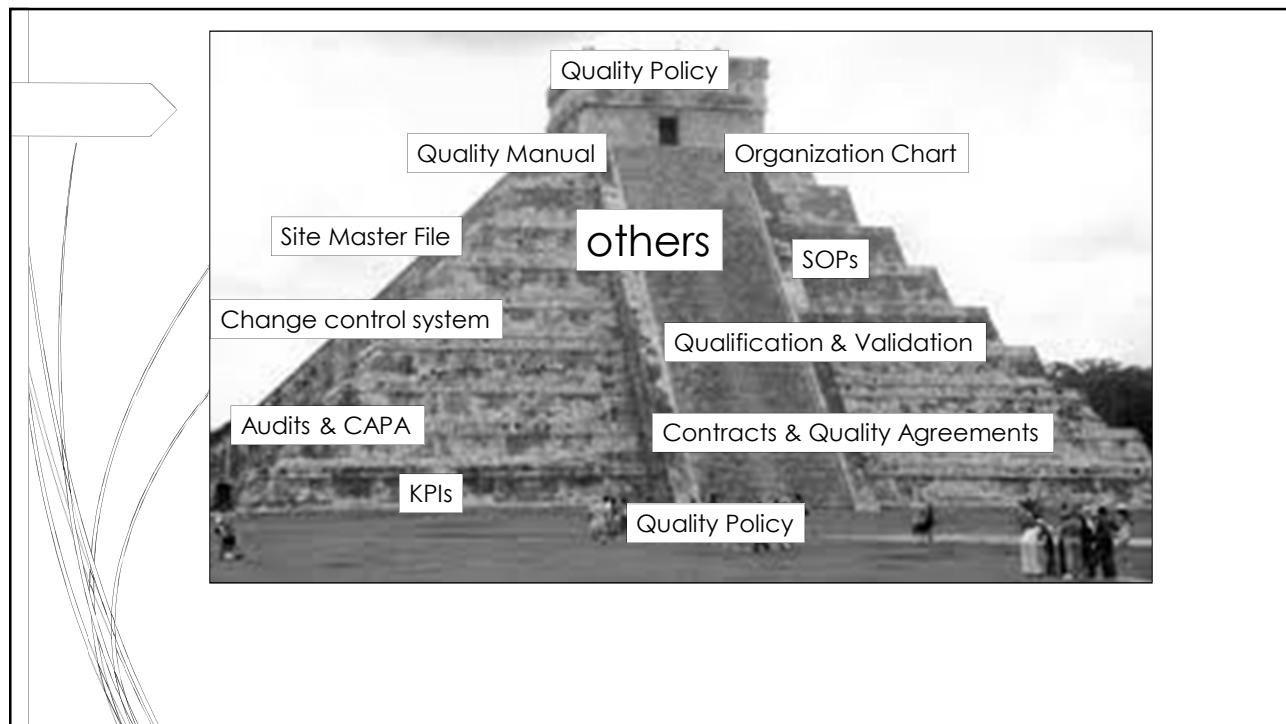
Document inventory and reconciliation: archiving and recovery

Document inventory and reconciliation

- List of main documents
- Documentation SOP
- SOP of SOPs
 - Version management
 - Current
 - Obsolete
- Where they are kept
- How to demonstrate traceability and recovery?

As per WHO GDocP&DI guideline

- data governance. The totality of arrangements to ensure that data, irrespective of the format in which they are generated, are recorded, processed, retained and used to ensure a complete, consistent and accurate record throughout the data life cycle.



Archiving and recovery

- Data retention may be for archiving (protected data for long-term storage) or backup (data for the purposes of disaster recovery).
- Data (or a true copy) generated in paper format may be retained by using a validated scanning process
- Procedures for destruction in accordance to QRM and legislative retention requirements.

Archiving and recovery

■ Archive

- A designated secure area or facility (e.g. cabinet, room, building or computerised system) for the long term, retention of data and metadata for the purposes of verification of the process or activity.
- Archived records may be the original record or a 'true copy' and should be protected so they cannot be altered or deleted without detection and protected against any accidental damage such as fire or pest.
- Legacy systems can no longer be supported, consideration should be given to maintaining the software for data accessibility purposes (for as long possible depending upon the specific retention requirements): virtual environment.
- Migration process

Archiving and recovery

- **Established procedures and train should ensure that data of appropriate accuracy, completeness, content and meaning are collected and retained for their intended use: dynamic storage & static**

■ Backup

- A copy of current (*editable*) data, metadata and system configuration settings maintained for recovery including disaster recovery.
- Backup and recovery processes should be validated and periodically tested.
- Backups for recovery purposes do not replace the need for the long term, retention of data and metadata in its final form for the purposes of verification of the process or activity.

GMP requirements vs. Knowledge Management

■ GMP requirements:

- GDocP&DI including QRM principles that assure the validity, completeness and reliability of data;
- By implementing quality metrics, also through PPQR
- CAPA plans follow up on deviations in GDocP&DI

■ Knowledge management and Company performance:

- Training
- To avoid fair
- Assurance that personnel are not subject to commercial, political, financial and other organizational pressures or incentives that may adversely affect the quality and integrity of their work
- Allocation of adequate human and technical resources for data generation and record keeping do not increase errors

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Developing Countries Vaccine
Manufacturers Network



coffee break





Exercise: BR review: traceability and data integrity

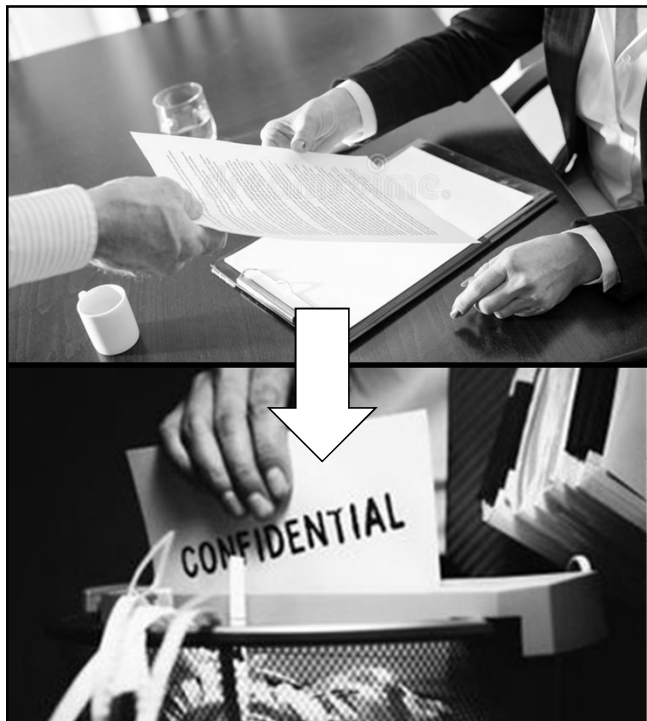
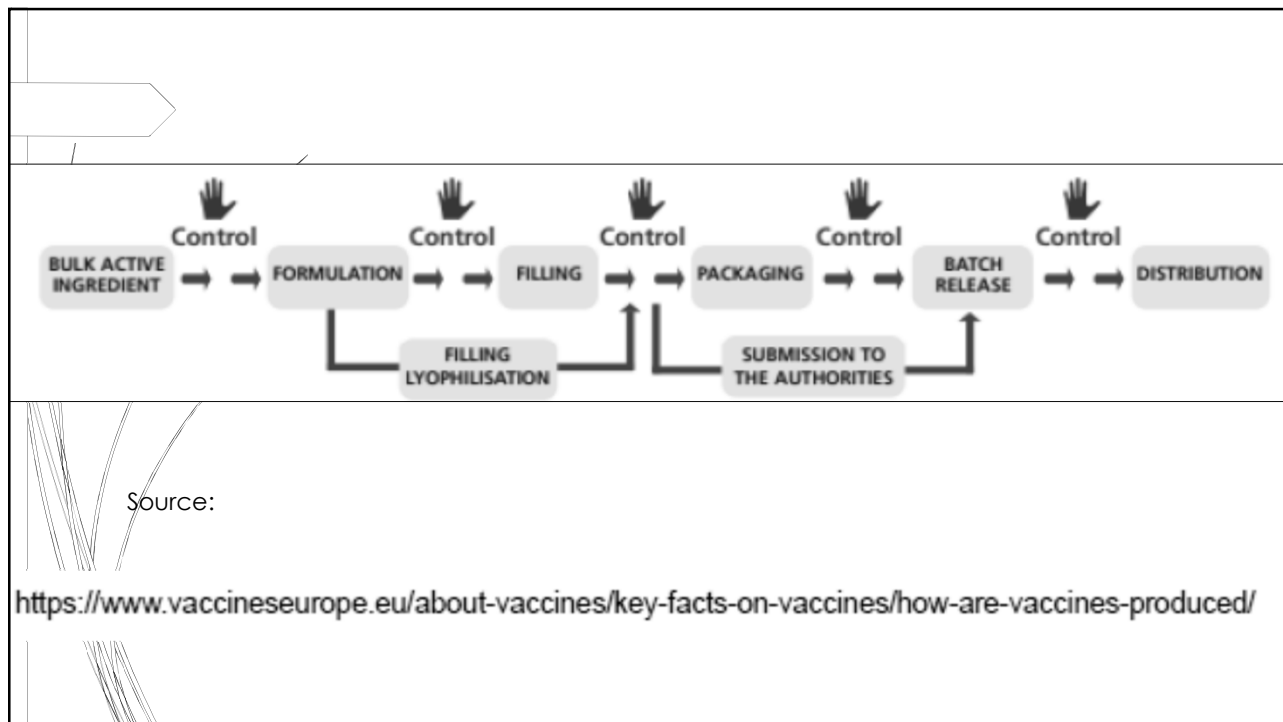


Some times you can find...



Diapositiva 63

sor1 sandra olga rumiano, 26/05/2018



Records –
Life Cycle
and data
integrity
issues

- EMA 'Data lifecycle' refers to how data is generated, processed, reported, checked, used for decision-making, stored and finally discarded at the end of the retention period, including interchange between Organization.
- WHO includes in Data life cycle the Validation for assessing risk and developing quality risk mitigation strategies for the data life cycle, including controls to prevent and detect risks throughout the steps of:
 - data generation and capture;
 - data transmission;
 - data processing;
 - data review;
 - data reporting, including handling of invalid and atypical data;
 - data retention and retrieval;
 - data disposal.

- Activities might include, but are not limited to:
- determining the risk-based approach to reviewing electronic data and audit trails based upon process understanding and knowledge of potential impact on products and patients;
- writing SOPs defining review of original electronic records and including meaningful metadata such as audit trails and review of any associated printouts or PDF records;
- documenting the system architecture and data flow, including the flow of electronic data and all associated metadata, from the point of creation through archival and retrieval;
- ensuring that the relationships between data and metadata are maintained intact throughout the data life cycle.
- SOPs and training. The validation activities should ensure that adequate training and procedures are developed prior to release of the system for GXP use. These should address:
 - computerized systems administration;
 - computerized systems use;
 - review of electronic data and meaningful metadata, such as audit trails, including training that may be required in system features that enable users to efficiently and effectively process data and review electronic data and metadata.
- Other validation controls to ensure good data management for both electronic data and associated paper data should be implemented as deemed appropriate for the system type and its intended use.

Supply Chain

All actors in the supply chain play an important part in overall data integrity and assurance of product quality.

Data governance systems should be implemented from the manufacture of starting materials right through to the delivery of medicinal products to persons authorised or entitled to supply medicinal products to the public.

Responsibilities should be documented in the contracts between the relevant parties.

Final responsibility of ensuring compliance throughout the supply chain rests with batch certifying AP/RP/QP

GMP Record Lifecycle

GMP Documents must be controlled, therefore, they require:

Controlled distribution circuit.

Controlled copies: copies of the controlled documents authorized by DT and / or Quality Guarantee to be delivered to the user responsible for the execution of the process or control of the system contemplated therein.

The documents must be modified after impact analysis, by exchange control system or revision for purposes of clarification / verification / expected expiration.

The documents must not be modified without prior authorization within the framework of the Quality System

The documents must not be overwritten or contain manuscript annotations or clarifications that escape the original content (for example, modifications of analytical techniques in the laboratory outside the Quality System made by analysts based on the experience of daily work or the simplification of calculations).

The documents must not have ambiguous contents: the title, objective, scope and procedure must be clearly stipulated.

They should be written in an orderly style and be verifiable, easy to understand and provide training.

Reproductions of working documents from master documents must have traceability of the source document and be verified to ensure that the original information was not modified / adulterated.

GMP Documents must be controlled, therefore, they require:

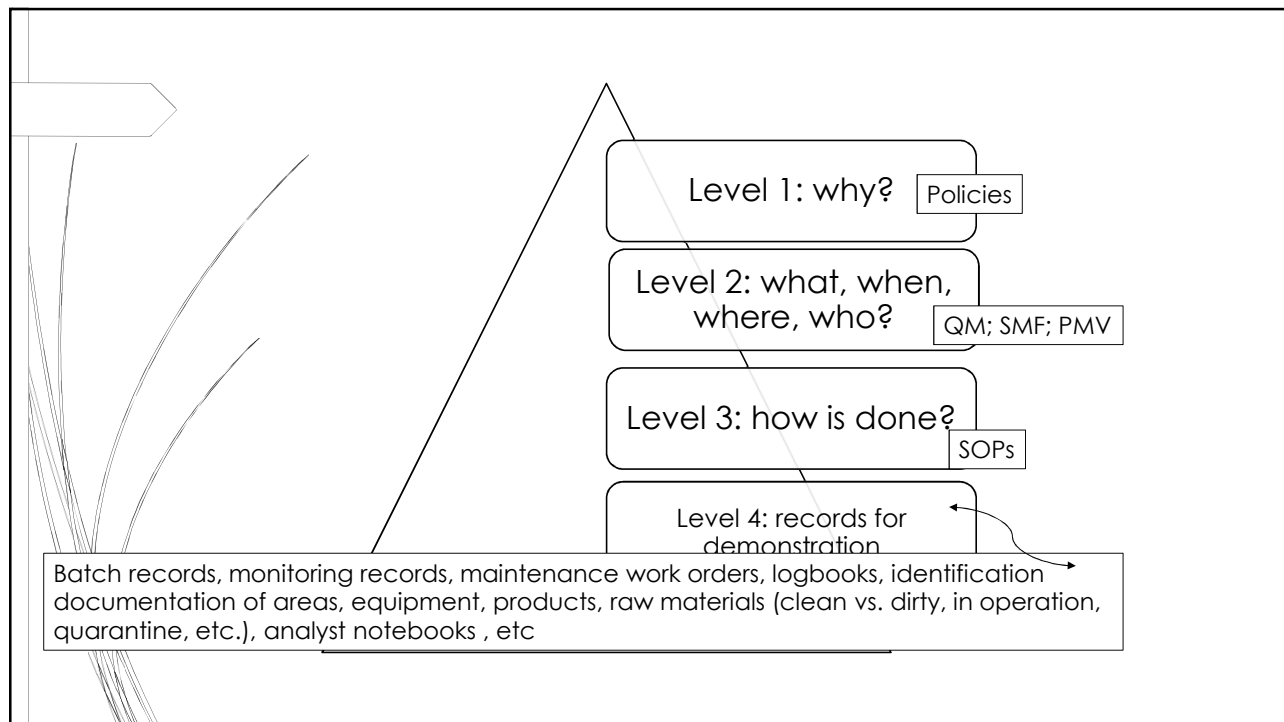
The replaced documents must be retained for a specified period of time, it is recommended at least one year after the expiration of the last product that has been manufactured based on the document in force at the time of manufacture / process.

When the documents require data registration, they must be clear, legible and made in an indelible blue color. It must be provided in the design with enough space for the records.

Electronic data processing systems, photographic media, or other reliable means of conserving documentation may be used.

Documents must be available at the place of use.

Documents stored electronically must be protected by means of a back-up or magnetic tapes, microfilms, paper prints or other means and upon request.




Example	Revision frequency	Lifecycle
Quality / Environmental Policy / Social / Documentary Quality Manual Master File of the Site Organization chart	Upon request Every 2 years Every year Upon request	1 Year and keeping last version and follow up at least as pdf
Legal documentation Contracts Regulatory Document Marketing authorization	Upon request	Till product involved is discontinued + n years
Training Plan/Capacitation program/ Calibration Plan Preventive Maintenance Plan Internal audits plan External audits plan	1/year	1 Year and keeping last version and follow up at least as pdf
SOPs	Every 2-3 years	1 Year and keeping last version and follow up at least as pdf
BR and analystys logoboks	Upon request	1 Year and keeping last version and follow up at least as pdf after product expiration, 10 years in some Companies



Control Mechanisms

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- Real time quality reviews
 - ALCOA challenge on document review
 - Risk management training on GDocP&DI
 - Audit trails challenge
 - Root cause on
 - Trends on Overwriting
 - Trends of Aborting runs
 - Trends on Deleting
 - Altering data trending
 - Human factors management
 - Review & Audits on:
 - Written procedures
 - Training programs
 - Record review & maintenance
 - Audits & self-inspections of governing processes

- 
- Backdating & recovery systems challenge
 - Human behavior
 - Ethics declaration and codes of conduct
 - Alone vs groups
 - How to manage the ethics compliance: HR or GC???
 - Factor for data governance success:
 - As part of PQS
 - Job description
 - Contracts
 - Challenge on recovery
 - Automatic data capture evaluation and implementation



Control Mechanisms





Exercise:
internal audit process
practice: instruction:
follow the supply chain
prepare the Audit /area

Source: Thesis in SCM as competitive advantage Dr. Sandra O. Rumiano

Ejemplo Industria Farmacéutica: por qué ella?




Exercise:
internal audit process
practice: examples for
the role play: addressing
ALCOA inside



Presentation
of results by
each working
group
(10 mins)



Conclusions & Adjourn

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- Importance of Quality Culture
 - Creating a data culture
 - To be collaborative on internal and external training
 - To assure to be trust
 - For the patients that depend on us to do it right.



On behalf of dcvmn

Thank You!

Dr. Sandra O. Rumiano