U.S. FOOD & DRUG ADMINISTRATION

Compounding Quality Center of Excellence Annual Conference

September 11, 2023

Quality Essentials: Inspectional Coverage of QMS and Data Integrity

Presented by: Jose Lopez, Program Expert, DPQB

The Impact of Quality On All Areas of Operation

Quality should be the foundation of all areas of a firm's operations. Quality is not the job of some, but the core of how all systems within a firm operate

Quality is not a standalone function, and it should be built into product. In this presentation, we will discuss how quality affects all operations and how all operations affect quality. Since quality is the foundation of all operations, QMS and quality thinking is integrated into all aspects of the company.

A few examples of quality-related controls that should be in place throughout a manufacturing process include, but are not limited to:

- Materials received from approved suppliers conform to specifications prior to use
- Materials are traceable from receipt through distribution
- Materials maintain their identity, safety, and purity throughout the process
- In-process control results conform to specifications
- Uncontrolled / unapproved reprocessing and rework are not performed
- Materials are handled safely and in a manner that prevents cross-contamination
- Manufacturing, testing, and packaging operations are conducted under the applicable requirements
- Finished drug product test results conform to specification at the time of release and throughout the assigned expiry
- Products are released only after authorization by the Quality Unit

A Basic Approach to Quality

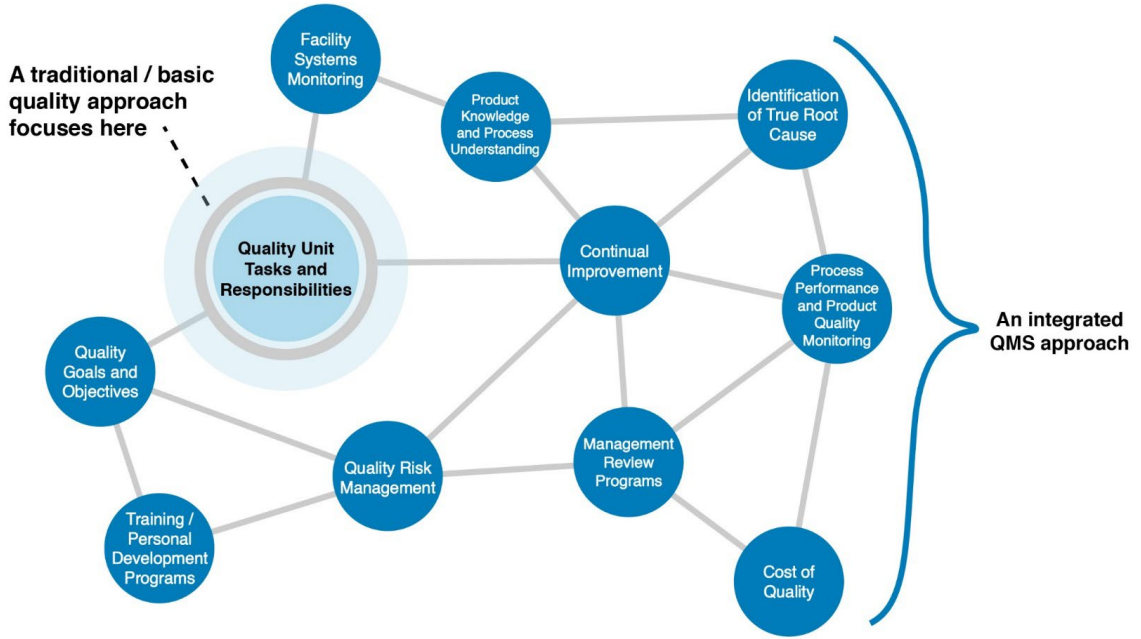
This presentation will take a more comprehensive view of quality, beyond just the typical tasks and responsibilities of the Quality Unit.

References:

- International Organization for Standardization (ISO) 9001:2015 Quality Management Systems – Fundamentals and Vocabulary
- Taiwan PDA, 2018 “Aspiring to Measure Quality Culture” Presentation, Cylia Che Ooi

A Comprehensive Approach to QMS

An integrated approach to QMS includes systems and processes that require participation of other functional units beyond quality, such as the manufacturing department, the validation department, and human resources. Understanding and managing interrelated processes as one system leads to more effectiveness and better efficiency in achieving your goals of producing quality products for your customers. This approach will help your organization control the relationships and interdependencies among the various processes, so that overall performance can be enhanced.



References:

International Organization for Standardization (ISO) 9001:2015 Quality Management Systems – Fundamentals and Vocabulary

Taiwan PDA, 2018 “Aspiring to Measure Quality Culture” Presentation, Cylia Chen-Ooi

Risk Based Inspections

- Outsourcing facilities are subject to FDA inspections according to a risk-based schedule, specific adverse event reporting requirements, and other conditions that help to mitigate the risks of the drugs they compound.
- Compounded drugs present a potential higher risk to patients than approved drugs. Compounded drugs are not FDA-approved and have not been reviewed by the Agency for safety, effectiveness, or quality before they are marketed.

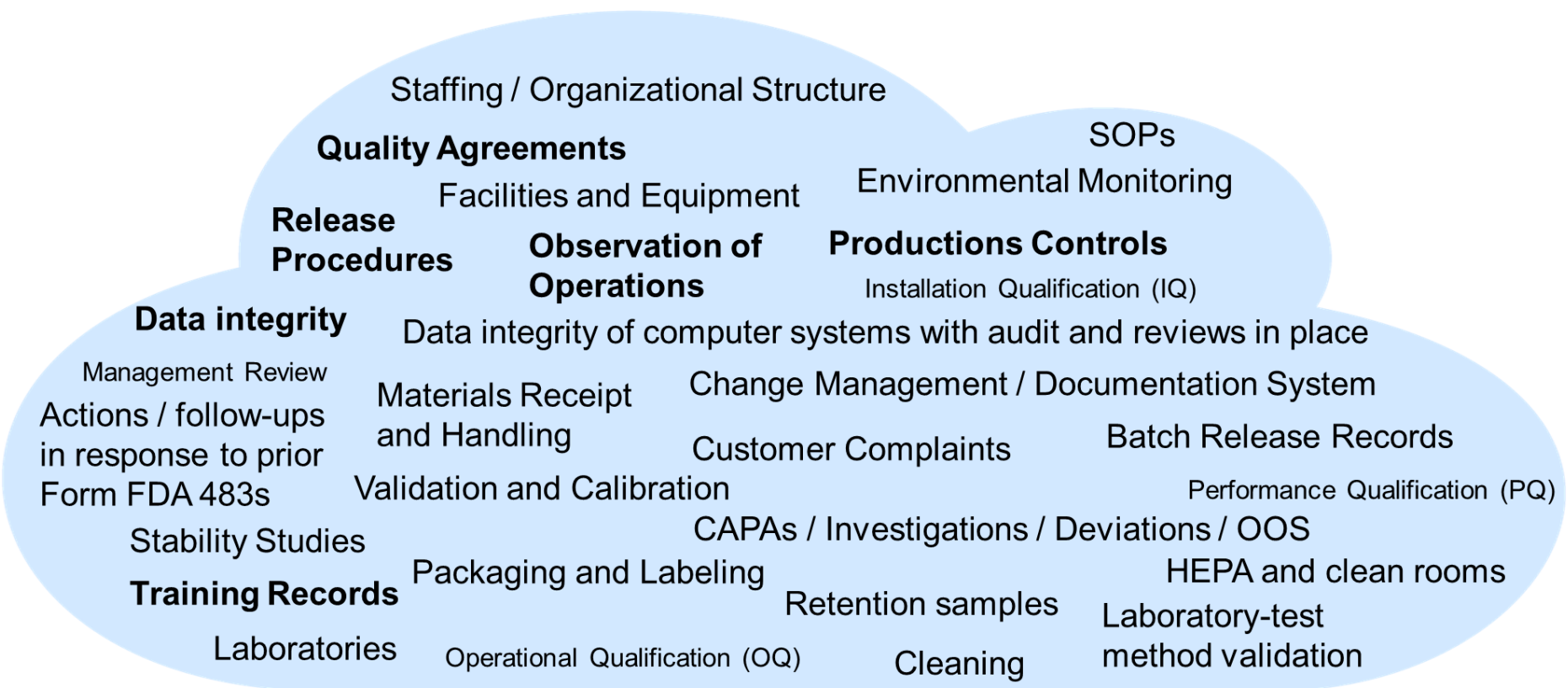
The Purpose of the Inspection

- The purpose of the inspection is to assess the outsourcing facility's compliance with CGMP, evaluate for insanitary conditions, and to evaluate whether the compounded drugs are meeting the conditions (including labeling, see 503B(a)(10)) and outsourcing facilities are meeting the requirements of section 503B, (including adverse event reporting, see 503B(b)(5)).

Reference:

FDA Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations

What Is Covered During An FDA Inspection (1 of 2)



What Is Covered During An FDA Inspection (2 of 2)

This list is not all-inclusive, but it contains documents and procedures that are generally reviewed during inspections.

Some aspects of facilities that are important to look at include warehouse operations, temperature control, water systems, floors and ceilings, lighting, air flow, and high efficiency particulate air (HEPA) filter maintenance.

When laboratories are reviewed, this may include equipment qualification, handling and control of samples, and control over data (data integrity). It is also important to make sure appropriate standards, like maintenance and calibration, are considered with equipment.

When reviewing change management and documentation systems, make sure to look for the schedule for SOP review, training records, and what training is performed.

A review of CAPAs and deviations is important as well. How many outstanding CAPAs do you have? Have you figured out root cause? Have you implemented the corrective action? Have you implemented the preventive action? Have investigations been thoroughly conducted? How many open deviations have you had? What is the outcome of those? OOS procedures will also be considered.

When looking at customer complaints, an inspection should look to understand whether issues have been addressed, customers have been responded to, and investigations have been initiated and are of appropriate scope.

Release procedures are looked at to make sure all appropriate documentation was reviewed.

An organization chart should be looked at to see whether the firm is appropriately staffed and whether an independent reporting structure exists for the QU.

A review of equipment may focus on cleaning procedures, whether equipment was properly installed, whether all IQ, OQ, and PQ have been performed, and whether there is an equipment maintenance schedule.

Management review should also be looked at. Are appropriate topics coming up in management review? Does issue elevation exist, and is it encouraged?

The investigator will want to see the manufacturing process real time. They will want to observe your operations. You should think about how to allow inspectors to view your operations real time, which may be with a glass partition or with a video camera.

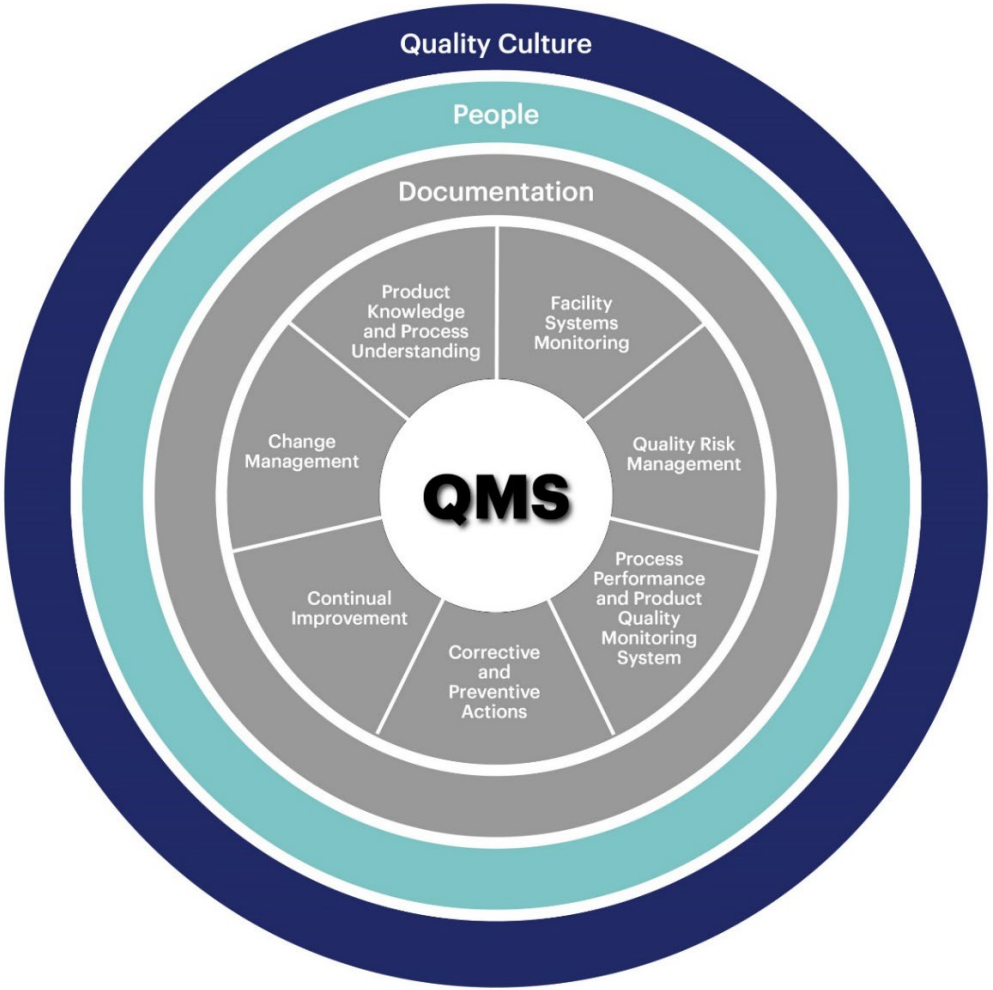
- Tangible Elements Considered:
- Quality Systems
- Packaging / Labeling
- Suppliers / Materials Controls
- Facilities / Equipment
- Training
- Complaints

Reference:

S. Schniepp

How Investigators Evaluate Quality/QMS During Inspections

QMS


Quality Culture
People
Documentation
Product Knowledge and Process Understanding
Facility Systems Monitoring
Change Management
QMS
Quality Risk Management
Continual Improvement
Process Performance and Product Quality Monitoring System
Corrective and Preventive Actions

Quality Culture and People

- Everyone in the organization is responsible for quality
- Quality Culture starts at the top and affects all aspects of the organization
- Quality Unit and Operations must be independent from each other
- Senior management is responsible for establishing a culture within an organization that focuses on quality
- Primary responsibilities of the Quality Unit are defined in 21 CFR 211
- Quality Unit oversees processes, procedures, and systems established to ensure patient safety and product quality
- QC focuses on meeting established quality criteria
- QA focuses on ensuring confidence that quality requirements are being met

Documentation

- Documentation of QMS is necessary to help support and demonstrate a comprehensive and integrated QMS. This can be done using a Quality Manual or equivalent approach.
    - In the Quality Manual, descriptions of the quality policy along with the scope of QMS and management responsibilities should be included.
- Documentation within QMS is done via each of the processes within QMS and their own procedures and associated records.
- Some QMS documentation is not process-specific. An example is the Master Validation Plan which provides details on how the organization will conduct validation activities and who is responsible for conducting these activities.
- SOPs should be written to achieve uniformity and be based on your specific operations.
- All documentation should follow good documentation practices.

Processes

- While their impact on organizations is separate, the following processes work together within an integrated QMS:
    - Product Knowledge and Process Understanding
    - Process Performance and Product Quality Monitoring
    - Facility Systems Monitoring
    - Quality Risk Management
    - Change Management
    - Continual Improvement
- Product knowledge and process understanding along with ongoing monitoring activities (i.e., process performance, product quality, and facility systems) ensure organizations are driving continual improvement.
- QRM ensures that scientifically based risk assessments are conducted to ensure the safety and quality of drug products.
- Change management establishes best practices for implementing changes within organizations.
- Continual improvement is critical to an organization's ability to reduce variability and increase efficiency.

Manufacturing Systems

Drug products are produced using many physical operations that bring together components, and containers and closures to make a product that is released for distribution. Historically, drug manufacturing has been organized into sets of operations and related activities called systems. During an inspection the investigator will cover elements of each of the systems.

- Control of all systems helps to ensure the firm will produce quality drugs, have the identity and strength purported, and meet the quality and purity characteristics that they are represented to possess.
- Focusing on systems will increase efficiency in conducting inspections because the systems are often applicable to multiple drug products.

The organization and personnel, including appropriate qualifications and training, employed in any given system, will be evaluated as part of that system's operation. Production, control, and distribution records required to be maintained by the CGMP regulations and selected for review should be included for inspection audit within the context of each of the systems.

State of Control

An Outsourcing Facility is considered to be operating in a state of control when it employs conditions and practices that assure compliance with Sections 503B, 501(a)(2)(A) of the Act, and Section 501(a)(2)(B). A firm in a state of control produces finished drug products for which there is an adequate level of assurance of quality, strength, identity and purity.

Inspectional Coverage of the Quality System (1 of 2)

- The quality system refers to the system (i.e., policies, procedures, controls, activities, etc.) satisfying the specific quality control and quality assurance requirements outlined under 21 CFR 211.22, as well as other quality-related requirements in 21 CFR part 211 and under the FD&C Act.
- The quality system should provide for effective senior management oversight of drug quality and support the establishment's quality unit. This includes, but is not limited to, quality policies, quality planning, quality resource management, and quality management review.

Inspectional Coverage of the Quality System (2 of 2)

- Assessment of the Quality System is two-phased. The first phase is to evaluate whether the Quality Unit has fulfilled the responsibility to review and approve all procedures related to production, quality control, and quality assurance and assure the procedures are adequate for their intended use as outlined under 21 CFR 211.22(a) and 211.22(c). This also includes the associated recordkeeping systems. The second phase is to assess the data collected to identify quality problems which may link to other major systems for inspectional coverage.

Written, Approved Procedures And Documentation

- For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. These areas are not limited to finished products but may also incorporate components and in-process materials.

Quality System: Written, Approved Procedures And Documentation (1 of 16)

Product Reviews

- The quality control unit must periodically (at least annually) review records of compounding operations to evaluate the quality standards for each drug product. Product reviews should include information from areas listed below as appropriate; batches reviewed, for each product, are representative of all batches produced; trends are identified; refer to 21 CFR 211.180(e)

Citation Example

- "Specifically, your firm did not conduct an annual product review (APR) for any drug products in 2021. The APR … consisted of a review of three (3) batch records for each product regardless of the number of batches made during the year, and did not include a review of all quality information related to the product ... Your firm is not reviewing quality metrics for the entirety of products made over the period of review such as complaints, deviations, and finished product testing."

Quality System: Written, Approved Procedures And Documentation (2 of 16)

Complaint Reviews

- (Quality and Medical): documented; evaluated; investigated in a timely manner; includes corrective action where appropriate
- Outsourcing facilities must have procedures for handling complaints that they receive about their compounded drug products.
- Written and oral complaints concerning the quality or purity of a drug product must be reviewed by the quality control unit, which must determine the need to investigate the complaint in accordance with § 211.192.
- Complaint handling procedures must include provisions for review to determine whether the complaint represents an adverse event that must be reported to FDA.

Adverse Event Reporting

- The firm should have adequate written processes for the surveillance, receipt, evaluation, and reporting of adverse events for the drug products it compounds.
- The firm should collect, process, and submit accurate and complete adverse event reports to FDA in a timely manner.
- The report should have the four required elements (identifiable patient, identifiable reporter, suspect drug, and serious adverse event).
- The firm must submit serious and unexpected reports as expedited reports to FDA as soon as possible, but no later than 15 calendar days after first receiving information.

Quality System: Written, Approved Procedures And Documentation (3 of 16)

Complaint Reviews / AE Reporting: Citations

- "Specifically, your procedure for handling complaints and recalls is deficient in that it does not include:
    1. Criteria for determination of whether the complaint represents an unexpected adverse event or a serious adverse event which requires reporting to the FDA.
    2. Provisions to review the possible failure of the drug product to meet its specification.
    3. Determination to conduct an investigation and extend to related drug if necessary."
- "Your firm does not follow your Complaint procedure… There were consumer complaints that did not have a conclusion, were not properly documented, not adequately investigated, and/or have not been closed within the established timeframe from initial complaint receipt."

Quality System: Written, Approved Procedures And Documentation (4 of 16)

Investigations of Discrepancies

- Discrepancy and failure investigations related to production and testing: documented; evaluated; investigated in a timely manner; includes corrective action where appropriate
- Results of tests and examinations, regardless of batch disposition, if applicable to evaluate the quality of components, containers, closures, in-process materials, and finished product. Depending upon the required critical quality attributes of the formulations, examples of such tests and examinations may include, but are not limited to, sterility testings; endotoxin levels; content assay; impurity assay; particulate matter; reconstitution time; content uniformity; preservative content testing; microbial enumeration; tests for specified microorganism; and, weight, volume, or counts.

Quality System: Written, approved procedures and documentation (5 of 16)

Investigations of Discrepancies: Citations

- Your firm rejected two lots of *drug product* following low potency assay at 89.7%, and 89.01%, specification 90.0-110.0%). Your corrective action was to increase active ingredient overage from 10% to 20% and to reduce the autoclave cycle; However, your firm has still not evaluated the effect this change has on potency loss and degradation on product quality, including an evaluation of impurities and the establishment of scientifically justified impurity limits.
- Your *drug product* suspension for Injection also failed potency specifications at 110.49%, specification 90.0-110.0%. The cause was associated with an extra 10% weighing of API to compensate for loss of potency in manufacturing. This overage has currently been adjusted to 5%, the impact of which has not been further assessed.
- Your firm rejected 5 lots due to presence of low CFU of objectionable microorganisms in ISO 8 air samples and the investigations lack rationale for not further evaluating lots manufactured prior and after the microbial detections.

Quality System: Written, Approved Procedures And Documentation (6 of 16)

Contract Laboratories

- Tests performed by a contract laboratory(s); name/location of laboratory(s); how the firm uses results from a contract laboratory(s) (e.g., does the firm wait for test results before shipping products); what materials are sent to the contract laboratory with samples (including labeling and description of the product).

Citation

- "Your firm failed to fully investigate an out of specification potency test result for drug product X. Your contract laboratory reported a result of 89.4%, outside the specifications of 90.0-115.0%. You reported this failure as a major deviation in the risk assessment. The quality unit approved this product for release… without proper justification to the investigation and there was no additional follow up with any associated batches. The batch was distributed…"

Quality System: Written, Approved Procedures And Documentation (7 of 16)

Change Control

- Documented; evaluated; approved; need for revalidation assessed

Citation

Your firm failed to adequately implement your firm's change control procedure… for changes made to approved protocols. For example;

1. During a review of your firm's performance qualification report, …Vial Washer Performance Qualification Report, I found your firm made changes to the protocol reporting section without initiating a change control and receiving approval to revise the original approved protocol.
2. Your firm's quality unit made changes to the acceptance criteria documented within the original protocol without obtaining your firm's management approval prior to its implementation and ultimate approval of the performance qualification.

Quality System: Written, Approved Procedures And Documentation (8 of 16)

Environmental Monitoring

- Environmental (microbial/viable and particle/non-viable counts) and personnel monitoring results including those that exceed alert or action limits and their associated trending data.

Citation

"Your firm has not conducted investigations into the majority of environmental monitoring and personnel monitoring excursions (recovery of organisms) identified as occurring in the ISO 5 environment. Your firm had approximately 1686 instances of excursions related to work performed in the ISO 5 area to include personnel monitoring, viable air and viable surface samples."

Quality System: Written, Approved Procedures And Documentation (9 of 16)

Environmental Monitoring

- The firm's methods, frequency, and locations for conducting environmental monitoring of air, surfaces, and personnel (operators' gloves).

Quality System: Written, Approved Procedures And Documentation (10 of 16)

Environmental Monitoring: Citations

- "Your firm has no documented justification for not monitoring all critical sites within the ISO 5 cleanroom where drug products are aseptically filled and/or lyophilized, ensuring the location monitored is providing a meaningful sample, and ensuring all locations are sampled at appropriate frequencies. For example,
- For product that is aseptically filled using the filling machine, viable active air sampling is not performed within the filling cabinet where open vials exit the depyrogenation oven and are filled and stoppered. The sample is taken from a table outside and behind the filling machine. One surface sample is taken of one of seven sampling sites identified within the ISO 5 filling machine before and after filling. The procedure does not define how to choose which site to sample. Your firm has no documented justification for sampling only one site.
- In addition, there is no non-viable particle monitoring in the vicinity of the table where open vials are filled and partially stoppered (lyophilized products). Your firm is relying on the non-viable particle counter for the ISO 5 cleanroom, which is located approximately 15 feet from where the filling of the lyophilized products occurs."

Quality System: Written, Approved Procedures And Documentation (11 of 16)

Media Fills

All investigations involving media fills / process simulations including their associated procedures, protocols, results and summary reports.

Citation

“Specifically, media fills for the lyophilized drug product Injection do not simulate worst case. For example, your firm compounds solution to fill 2400 vials … and the entire 2400 vials are lyophilized at the same time. Your media fill is only simulating the filling of 800 vials... The media fill does not simulate the filling of the three sublots and placing all 2400 partially stoppered vials in the lyophilizer at the same time.”

Quality System: Written, Approved Procedures And Documentation (12 of 16)

Validated Methods /Equipment Malfunction

Process deviations from validated methods or equipment malfunctions that involve critical equipment, such as sterilizers and lyophilizers.

Citation

“Specifically, autoclave #X, which is used to sterilize equipment and utensils used in the processing of sterile drug products, has failed to complete its sterilization cycle on approximately 25% of runs since XX/XX/XX. You have not determined the root cause of the autoclave’s malfunctioning or had the autoclave repaired and you have continued to use the autoclave for sterilizing equipment and utensils used to process sterile drug products.”

“Evaluation of equipment such as sterilizing filters and container closures have not been evaluated adequately.”

Quality System: Written, Approved Procedures And Documentation (13 of 16)

Rejects

Investigation expanded where warranted; corrective action where appropriate

Citation

“Visual Inspection Rejects - Your firm does not conduct investigations into vials rejected during your 100% visual inspection process. Additionally, you have not established a reject limit for the number of vials that can be rejected for a given batch size. For example, your batch record for drug product X Preservative-Free Injection, documents 488 vials were visually rejected out of 888 filled vials. No investigation was conducted and the batch was released.”

Quality System: Written, Approved Procedures And Documentation (14 of 16)

Stability Failures

Investigation expanded when warranted; and disposition of product

Citation

“Out of Specification (OOS) Results - Investigations are not always conducted when products fail to meet your internal specification for potency, sterility, or bacterial endotoxin. Additionally, there has been no assessment of how these failures affect any previous or future production. The following are examples of commercial and stability batches that had OOS results associated with them.”

Quality System: Written, Approved Procedures And Documentation (15 of 16)

Validation

Status of required validation/ revalidation (e.g., computer, production process, laboratory methods)

Citation

“Process validation has not been performed for the any of the unique hormone pellets drug products manufactured on site. No procedures are established for the ongoing periodic monitoring of the drug manufacturing process.”

Quality System: Written, Approved Procedures And Documentation (16 of 16)

Training/Qualification

Training/qualification of employees in quality control unit functions

Citation

“Your firm's Quality Assurance Technician performed her duties prior to receiving and completing cGMP and Quality training courses.”

Characteristics of a Successful QMS

Successful quality management systems share the following characteristics:

- Approaches that are science-based
- Supportive management (philosophically and financially)
- Well-defined processes and products, starting from development and extending throughout the product lifecycle
- Decisions based on an understanding of the intended use of a product
- Sound methods for assessing and reducing risk
- Proper identification and control of areas of potential process weakness
- Responsive deviation and investigation systems that lead to timely remediation
- Systems for careful analysis of product quality

Reference:

FDA Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations

Data Integrity and Data Governance

Quality Culture Impacts Data Integrity

It is the role of senior management to create a Quality Culture where employees understand **that data integrity is an organizational core value** and employees are encouraged to identify and promptly **report data integrity issues**. In the absence of management support of a Quality Culture, quality systems can **break down** and lead to **CGMP noncompliance.**

One of the benefits of having a robust Quality Culture is that you can more easily avoid data integrity issues, which we will be discussing in this module. Please note, while data integrity is an absolute requirement and expectation in a positive Quality Culture, it is not the only thing you need to pay attention to for Quality Culture, as demonstrated in the previous module. It is only one element. So, what do we mean by "data integrity?"

Reference:

FDA Data Integrity and Compliance with Drug CGMP Guidance for Industry

Data Integrity

Data Integrity: The completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be Attributable, Legible, Contemporaneously Recorded, Original or a true copy, and Accurate (ALCOA).

Source: FDA Data Integrity and Compliance with Drug CGMP Questions and Answers Guidance for Industry

A critical aspect of proving that your product meets specifications and that your systems and facility are in a state of control is to ensure data integrity.

Data integrity is the assurance that data records are accurate, complete, intact, and maintained within their original context, including their relationship to other data records. This applies to data recorded in electronic and paper formats or a hybrid of both.

Reference:

FDA Guidance for Industry Data Integrity and Compliance with Drug CGMP

Why Is This Important?

Ensuring data integrity means protecting original data from accidental or intentional modification, falsification, or even deletion.

Regulatory Requirements Related to Data Integrity (1 of 2)

Requirements with respect to data integrity in parts 211 and 212 include, among other things:

Regulatory Requirements

- **§ 211.68** - Requiring that "backup data are exact and complete" and "secure from alteration, inadvertent erasures, or loss" and that "output from the computer … be checked for accuracy"
- **§ 212.110(b)** - Requiring that data be "stored to prevent deterioration or loss"
- **§§ 211.100** and **211.160** - Requiring that certain activities be "documented at the time of performance" and that laboratory controls be "scientifically sound"
- **§ 211.180** - Requiring that records be retained as "original records," or "true copies," or other "accurate reproductions of the original records"

References:

- 21 CFR 211.100
- 21 CFR 211.160
- 21 CFR 211.180
- 21 CFR 211.68
- 21 CFR 212.110(b)

Regulatory Requirements Related to Data Integrity (2 of 2)

Requirements with respect to data integrity in parts 211 and 212 include, among other things:

Regulatory Requirements

- **§§ 211.188**, **211.194**, and **212.60(g) -** Requiring "complete information," "complete data derived from all tests," "complete record of all data," and "complete records of all tests performed"
- **§§ 211.22**, **211.192**, and **211.194(a)** - Requiring that production and control records be "reviewed" and that laboratory records be "reviewed for accuracy, completeness, and compliance with established standards"
- **§§ 211.182**, **211.186(a)**, **211.188(b)(11)**, and **211.194(a)(8)** - Requiring that records be "checked," "verified," or "reviewed"

References:

- 21 CFR 211.182
- 21 CFR 211.186(a)
- 21 CFR 211.188
- 21 CFR 211.192
- 21 CFR 211.194
- 21 CFR 211.22
- 21 CFR 212.60(g)

Guidance on Data Integrity

FDA Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry

- Data integrity is critical throughout the CGMP data lifecycle, including in the **creation, modification, processing, maintenance, archival, retrieval, transmission,** and **disposition** of data after the record's retention period ends.
- System design and controls should enable easy **detection of errors, omissions, and aberrant results** throughout the data's lifecycle.

The CGMP Guidance for Data Integrity, which is set up as a Q&A document, also states, "For the purposes of this guidance, data integrity refers to the completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA)."

Data integrity should be upheld throughout the CGMP data lifecycle. Keeping thorough, accurate data is the proof that your facility is making quality products and using functional equipment. The data surrounding all equipment in use, or products produced, should be maintained for a certain amount of time with all associated metadata required to reconstruct CGMP activity. This certain amount of time is known as the retention period.

Data integrity is an integral aspect of QMS and is dependent on the careful handling of data and documents, including supporting information demonstrating product quality. The way in which data are treated, stored, and corrected is of the utmost importance because it is the proof to inspectors (clients, regulatory authorities, audits, etc.) that the product meets specifications and quality expectations. This is what you rely on. If you do not treat your data with respect, you do not have anything to fall back on. Data for products should be retained for at least one year after their expiration as required by 21 CFR 211.180(a). Equipment records should also be archived, but the retention period varies. After equipment is installed, operating, and maintained, any documentation that provides periodic evaluation should be archived in case the equipment needs to be decommissioned. Additionally, if a piece of equipment must be decommissioned before product it produced expires, the retention period will extend until the equipment is replaced AND the original product has expired.

References:

- S. Schniepp
- FDA Data Integrity and Compliance with Drug CGMP Guidance for Industry
- 21 CFR 211.180

Examples of Data Integrity Violations

- × Lack of Control over Data Changes / Manipulations
- × Inadequate Control Over Access to Data
- × Reporting Not Supported by Raw Data
- × Not Reporting All Data
- × Testing into Compliance by Rerunning Samples Until Results Pass
- × Misrepresenting Existing Data as New Data
- × Fabricating Data
- × Forging and / or Unauthorized Signatures
- × Not Recording Activities in Real-time
- × Discarding Data (Electronic or Hard Copy)
- × Altering Data (Electronic or Hard Copy)
- × Backdating

There is no distinction between benign data integrity violations and malicious violations. Benign violations still compromise the integrity of your data and your documents. No regulatory authority can inspect your intentions. If it is a benign negligence, and someone makes a mistake, it will still be considered a data integrity violation. When people make violations, no one ever writes down their intent, which is why intent is not inspected for.

Example of a benign data integrity violation: My boss is out of town and is the only one authorized to sign a certain type of report. However, we need the report signed because our production schedule will be delayed otherwise. I cannot reach my boss, but I have reviewed the report and had the errors corrected. The only thing lacking is the final signature, so I sign my boss's name. This is still bad, even though there was no malicious intent. The better way to handle this is for the boss to give temporary signing authority. It must be documented that this authority is given. Intent does not matter.

Reference: S. Schniepp

The ALCOA+ Framework (1 of 2)

The ALCOA+ Framework can be used to support good data integrity practices.

Data Integrity Element	Description	21 CFR* Reference
Attributable	All data generated or collected must be attributable to the person generating the data.	211.101(d), 211.122, 211.186, 211.188(b)(11)
Legible	All data recorded must be legible (readable) and permanent.	211.180(e)
Contemporaneous	Results, measurements, and data are recorded at the time the work is performed.	211.100(b) and 211.160(a)
Original	Original data, sometimes referred to as source data or primary data, is the medium in which the data point is recorded for the first time.	211.180 and 211.194(a)
Accurate	Data is complete, consistent, truthful, and representative of facts.	211.22(a), 211.68, 211.188

4 Additional Elements:

- **Complete:** Information that is critical to recreating and understanding an event. This would include any repeat or reanalysis performed on a laboratory test sample.
- **Consistent:** The data is presented, recorded, dated, or time-stamped in the expected and defined sequence.
- **Enduring:** The data or information must be maintained, intact, and accessible throughout their defined retention period.
- **Available:** The data or information must be able to be accessed at any time during the defined retention period.

*CFR stands for Code of Federal Regulations

The ALCOA+ Framework (2 of 2)

FDA uses the ALCOA framework to support good data integrity practices. The + sign in ALCOA refers to the four additional elements of ALCOA, which have been added because they speak to electronic systems and are becoming best practice for industry. They are covered in FDA's Data Integrity Guidance for Industry (GFI) (Complete, Consistent) and 21 CFR 211.68(b) and 21 CFR 211.180(c) (Enduring, Available). These additional elements are also covered in the most recent WHO (World Health Organization) guidance.

Each of the examples of data integrity violations listed on the previous slide 42, whether completed benignly or not, violate certain ALCOA principles that are addressed on this slide. The fabrication of data, for example, specifically violates the "contemporaneous," "original," and "accurate" elements of the ALCOA framework. Similarly, backdating violates the "contemporaneous" element and misrepresenting existing data as new violates the "original" element. Not reporting all data is typically seen in laboratories and violates the "accurate" and "complete" elements of ALCOA. Next, testing into compliance by rerunning samples would mean ignoring data that do not fit a specific conclusion and choosing only measurements that do fit. This is a clear violation of the "accurate" and "complete" elements of ALCOA+. Similarly, reporting not supported by raw data also violates the "accurate" element. An example of the "available" element, which is one of the four additional elements of ALCOA+ is inadequate control over access to data. In this case, it is necessary to have audit trails to track data changes. Another violation is forging and / or having unauthorized signatures. This violates the "attributable" element of ALCOA. Next, not reporting activities in real-time violates both the "contemporaneous" and "original" elements because results are not reported at the time they were performed. Discarding or altering data would violate both the "accurate" and "original" elements. Finally, lack of control over data changes / manipulations suggests that others are able to alter reported results, meaning this example would violate the "attributable," "accurate," and "original" elements. In this case, audit trails are essential and can prevent data changes / manipulations from occurring.

We encourage all the participants to go to the CFR and do their own research on ALCOA concepts.

One additional consideration for organizations that use electronic signatures and keep electronic records, you can refer to 21 CFR Part 11 and related GFI for the regulations and additional information on electronic records.

References:

- 21 CFR 211.180
- 21 CFR 211.68
- FDA Data Integrity and Compliance with Drug CGMP Guidance for Industry
- (WHO) Guidance on Data Integrity Draft for Comments

Data Integrity and Data Governance | Summary

- Data integrity and handling violations:
  - Compromise the product
  - Compromise CGMP
  - Raise concerns about company culture
  - Compromise trust in an organization and trust in specific individuals to perform their duties as required by the 21 CFR
  - Risk company reputation
  - Risk patient safety

- To ***prevent*** data integrity and handling violations:
  - Understand the regulatory requirements as stated in 21 CFR Part 211 (also Part 11 if applicable)
  - Become familiar with FDA guidance documents that describe current thinking on the topic
  - Document your practices in writing
  - Perform training annually and as needed
  - Perform formal risk assessments of all practices and procedures to identify risk to data
  - Continuously reinforce proper data integrity and handling practices through a strong Quality Culture

Data integrity and governance is something you need to constantly keep in mind. It should be and needs to be the company's daily way of operating, it is not just the responsibility of the QU. The concepts of appropriately handling data and keeping high levels of integrity with data need to be ingrained in the culture and everyone's attitudes. Tomorrow we will discuss what to do if a data integrity issue is found.

Reference: S. Schniepp


FDA
U.S. FOOD & DRUG
ADMINISTRATION