Quality Assurance in the Pharmaceutical Industry

27 February 2021

Quality Assurance in the Pharma Industry

"**Quality assurance**"

is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including product design and development.

" **Διασφάλιση ποιότητας**"
Ειναι μια ευρεία έννοια που καλύπτει όλα τα θέματα που επηρεάζουν μεμονωμένα ή συλλογικά την ποιότητα ενός προϊόντος.
Είναι το σύνολο των ρυθμίσεων που γίνονται με σκοπό να διασφαλιστεί ότι τα φαρμακευτικά προϊόντα εχουν την απαιτούμενη ποιότητα για την προοριζόμενη χρήση τους.
Η διασφάλιση ποιότητας συνεπώς ενσωματώνει τους κανόνες GMP καθώς και άλλους παράγοντες, συμπεριλαμβανομένου του σχεδιασμού και της ανάπτυξης προϊόντων.

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What is the regulatory frame?

https://ec.europa.eu/health/documents/eudralex/vol-4_en

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/directive-2001/83/ec-european-parliament-council-6-november-2001-community-code-relating-medicinal-products-human-use_en.pdf

https://www.ich.org/page/quality-guidelines

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What is captured in the law?

Licensed pharmaceutical products (marketing authorization) should be manufactured only by licensed manufacturers (holders of a manufacturing authorization) whose activities are regularly inspected by competent national authorities.

The manufacturers must operate within a defined regulatory frame.

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What is captured in the law?

The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate **safety, quality or efficacy**.

To achieve the quality objective reliably, there must be a comprehensively designed and correctly implemented system of quality assurance incorporating GMP and quality control. It should be fully documented and its effectiveness monitored.

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More in detail: EudraLex vol 4 / Chapter 2: Personnel

Senior Management should appoint Key Management Personnel including the **head of Production**, the **head of Quality Control**, and if at least one of these persons is not responsible for the duties described in Article 51 of Directive 2001/83/EC1, an adequate number, but at least one, **Qualified Person**(s) designated for the purpose.

Normally, key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other. In large organisations, it may be necessary to delegate some functions.

Additionally depending on the size and organisational structure of the company, a separate Head of Quality Assurance or Head of the Quality Unit may be appointed. Where such a function exists usually some of the responsibilities described in 2.7, 2.8 and 2.9 are shared with the Head of Quality Control and Head of Production and senior management should therefore take care that roles, responsibilities, and authorities are defined.

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- *According to Article 51 paragraph 3 of Directive 2001/83/EC), a **Qualified Person** must secure that*
- each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorisation

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It is not that simple!

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MANAGEMENT RESPONSIBILITY

- *Essential component; Not just about compliance*
  - Visible leadership to establish and maintain a company wide culture and commitment to Quality and improvement
  - Monitor performance of the PQS and act
  - Control of Internal and Outsourced activities
- *Quality cannot be owned by the Q Unit*
  - Management is accountable
  - independent assessments / audits are key

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ENABLERS OF THE QUALITY SYSTEM

✓Knowledge Management

Systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes and components. Sources of knowledge include, but are not limited to prior knowledge (public domain or internally documented) pharmaceutical development studies, technology transfer activities, process validation studies over the product lifecycle, manufacturing experience, innovation, continual improvement and change management activities

✓Quality Risk Management

It can provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality.

It facilitates continual improvement of process performance and product quality throughout the product lifecycle.

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ENABLERS OF THE QUALITY SYSTEM

✓Quality Culture

Quality culture is the mindset and behavior to consistently perform the right things in the design and execution of the quality management principles right first time. The quality culture is critical for the successful execution of business performance and strategy.

✓Data integrity

Data integrity is paramount to support the quality, safety and efficacy claims of our products. Quality is therefore engaged in fostering data integrity assurance at all levels in a company through implementation of quality standards during data lifecycle.

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4 MAIN ELEMENTS OF THE QUALITY SYSTEM

- ✓ **PROCESS PERFORMANCE AND PRODUCT MONITORING**
  - ensure a state of control is maintained.
  - identify areas for continual improvement

  A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality.

  The results of product and processes monitoring are taken into account in batch release, in the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future.
- ✓ **CAPA SYSTEM**

  CAPA methodology should result in product and process improvements and enhanced product and process understanding

  An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems. CAPA effectiveness is evaluated

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4 MAIN ELEMENTS OF THE QUALITY SYSTEM

- ✓ **CHANGE MANAGEMENT**

  The change management system ensures continual improvement is undertaken in a timely and effective manner. Change effectiveness is evaluated as required.

- ✓ **MANAGEMENT REVIEW**

  Management review provides assurance that process performance and product quality are managed over the lifecycle.
  Regularly scheduled reviews of quality management system against predefined objectives must be held. This will include an evaluation of the performance of the system based on existing data and address any decisions or actions necessary to improve the system and its related processes

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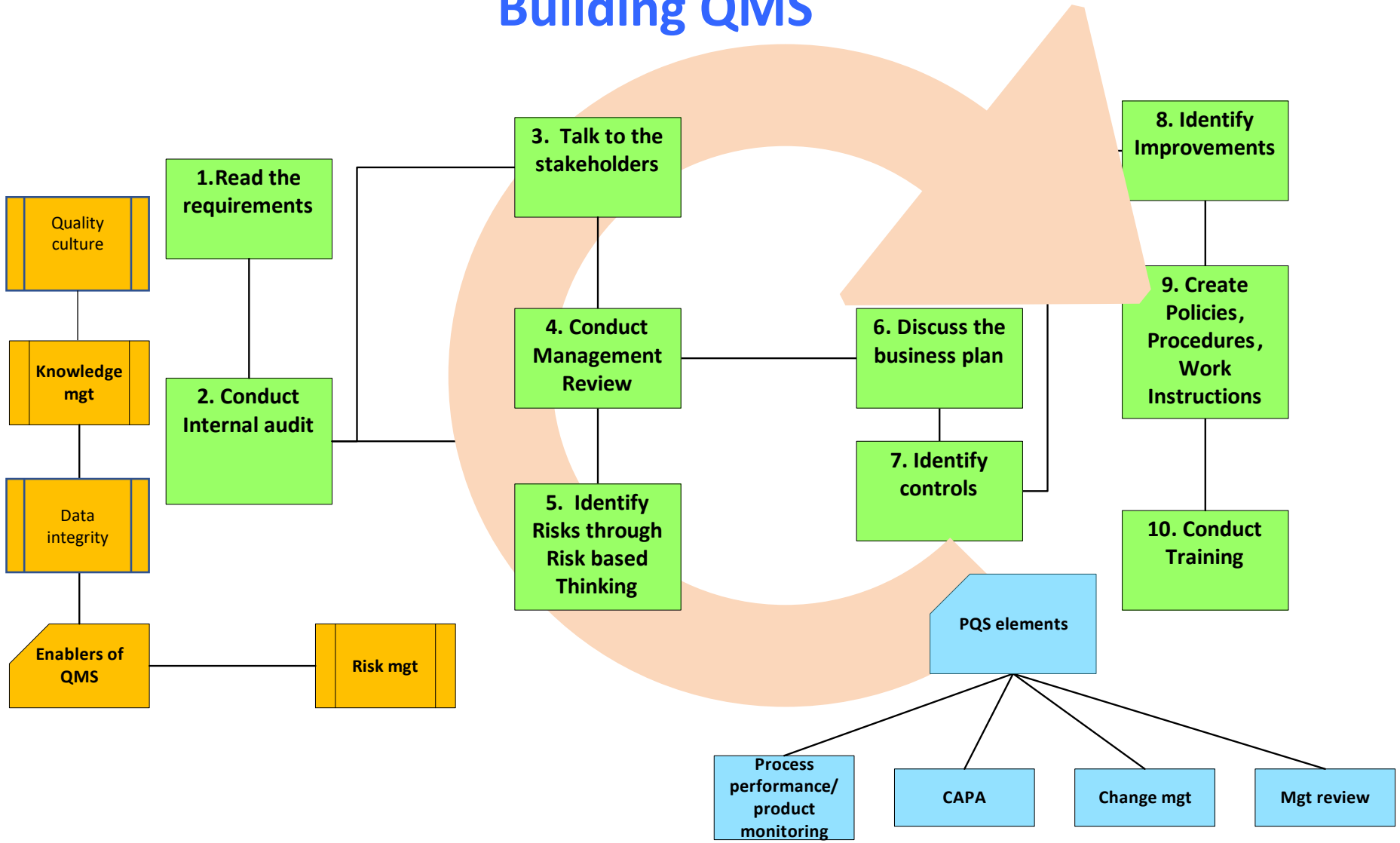
Building QMS



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Good manufacturing practices for pharmaceutical products (GMP)

- Sanitation and hygiene
- Qualification and validation
- Prevention of cross-contamination
- Cleaning validation
- Process validation
- Complaints
- Product recalls
- Internal/External audits
- Suppliers' audits and approval
- Personnel Training

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Premises

- Storage areas
- Weighing areas
- Production areas
- Quality control areas

Equipment

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Materials

- Starting materials
- Packaging materials
- Intermediate and bulk products
- Finished products
- Rejected, recovered, reprocessed and reworked materials
- Recalled products
- Returned goods
- Reference standards
- Waste materials

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Building of Documentation

Good practices in production

- Processing operations
- Packaging operations

Good practices in quality control

- Control of starting materials and intermediate, bulk and
- Finished products
- Test requirements

Batch record review

- Stability studies

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Qualification and Validation

Each pharmaceutical company should identify what qualification and validation work is required to prove that the critical aspects of their particular operation are controlled.

The key elements of a qualification and validation programme of a company should be clearly defined and documented in a Validation Master Plan.

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Qualification and validation should establish and provide documentary evidence that:

(a) the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP (design qualification, or DQ);

(b) the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications (installation qualification, or IQ);

(c) the premises, supporting utilities and equipment operate in accordance with their design specifications (operational qualification, or OQ);

(d) a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process validation, or PV, also called performance qualification, or PQ).

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Any aspect of operation, including significant changes to the premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, should be qualified and validated.
Qualification and validation should not be considered as one-off exercises. An ongoing programme should follow their first implementation and should be based at least on an annual review.

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Process validation

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Process validation is the collection and evaluation of data, from the process design stage through to production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process. The new approach for process validation describes process validation activities in three stages:

- **Stage 1** – Process design: The manufacturing process is established during this stage based on knowledge gained through development and scale-up activities.
- **Stage 2** – Process qualification (Process validation): During this stage, the process design is evaluated to determine if the process is capable of reproducible manufacturing.
- **Stage 3** – Continued process verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

Each manufacturing site should develop and maintain a site validation master plan (SVMP), which describes these validation approaches and strategies.

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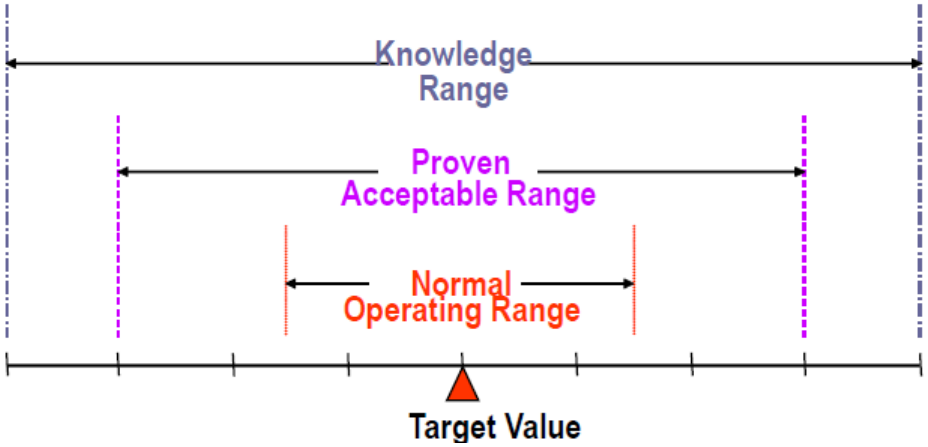
Process Validation Benefits to Industry

Knowledge vs. Proven Acceptable vs. Normal Operating Range

- Knowledge that the product will meet requirements
- Ability to predict product quality / assess impact of changes prior to OOS
- Reduced deviations – Reduce time to market, reduce release time
- More efficient / effective deviation resolution



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- **Process Validation**
- **Stage 1 Expectations**

1) Define risk based methodology and team structure
2) Define CQA
3) Perform Risk Assessment
4) Design of Experiments & Quality by Design
4) Define applicable CPP's
5) Determine analytical process variation
6) Demonstrate variation correlation
7) Establish control strategy
8) Assess data

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- **Process Validation**
- **Stage 2 Expectations**

1)Confirm Facility, Equipment, Utilities “fit for purpose” check

2)Develop PPQ Protocol including:

a) Definition of testing methodology and team structure

b) Definition of statistical terms and formulas

c) Applicable references to stage 1 summary report

d) Control strategy

e) Number of batches

f) Sampling Plan

g) Create control charts

h) Acceptance Criteria / Investigation process for both intra and inter batch variability.

I) Training record

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- **Process Validation**
- **Stage 2 Expectations (ctd)**
- 3) Train Operations and Analytical Team
- a) Manufacturing Processes
- b) Statistical Process Control trending or charting begins
- c) Updated SOP's
- d) Batch record review
- e) Risk assessment review
- f) CPP/CQA Matrix review
- 4)Execute Protocol
- 5)Revise risk assessment and CPP/CQA

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Process Validation

Stage 2 Expectations (ctd)

1) Summary of results

2) Confirm Process Performance value

3) List of CPP's by Risk Priority Number

4) Control system

5) Determine confidence intervals

6) Justification for reduced testing ("hand-shake" to Stage 3)

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Process Validation

Stage 3 Expectations

1)Establish an SOP / Methodology

2)Variable monitoring frequency, alert & action levels reviewed for ‘in-control’ approval

3) Revise Batch records

4) Revise CAPA / Change control process

5)Utilize CPP/CQA matrix including potential revision of alert & action levels

6) Record and trend CQA batch results

7) Report CQA trends

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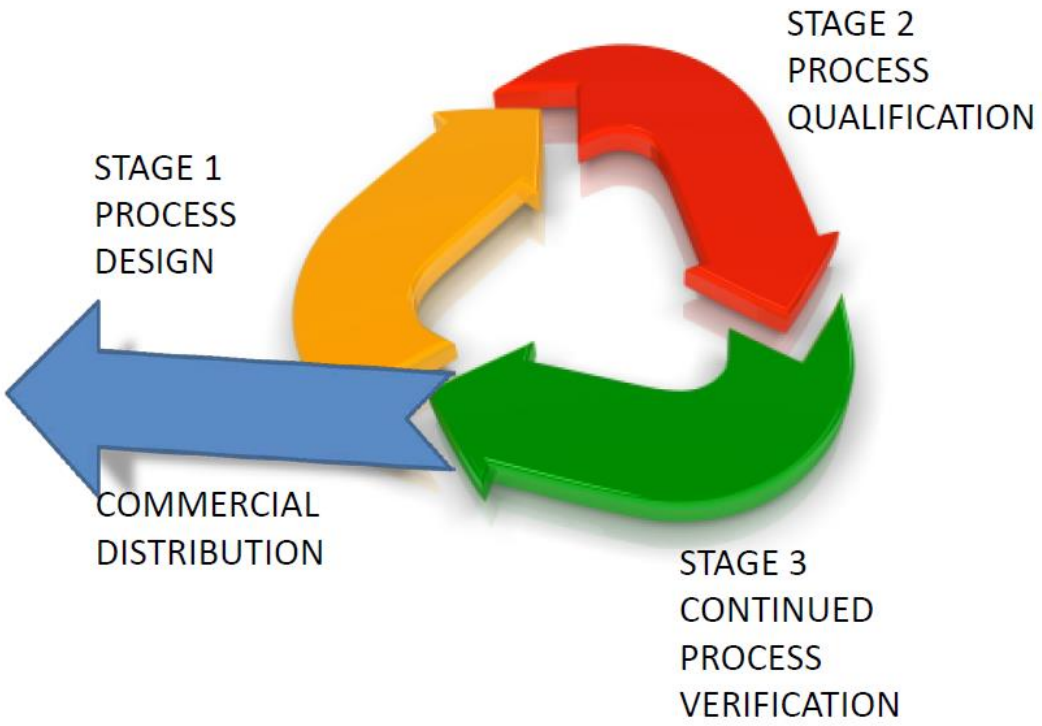
Lifecycle Staged Approach



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- **Cleaning Validation**

Each procedure used to clean product contact surface equipment must be validated, including manual, semi-automated and fully automated processes. Consideration should be given to the manufacturing and surrounding areas and to non-product contact parts into which product may migrate (for example, seals, flanges, mixing shaft, fans of ovens, heating elements etc.) in order to prevent contamination and cross-contamination in shared facilities.

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Cleaning Validation

- Scientific and risk-based rationale should be applied. The risk analysis should determine the level of the validation required for each cleaning procedure and should be based on the effects on the product quality and on the patients' safety. The following parameters should be considered in the risk assessment:
  - Solubility of the APIs in water (or in the solvent used in the cleaning procedure)
  - Toxicity and potency of the processed products
  - Cleanability of the processed soils
  - Equipment design and construction (the ease of cleaning of the product contact surfaces)
  - Dedicated / non-dedicated equipment

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Cleaning Validation

- Equipment trains
- Type of the cleaning (automated / manual) which has impact on the variability of the cleaning procedure
- Critical equipment parts
- Material/s of the equipment (adsorption on the surface)
- Manufacturing campaigns
- Batch sizes
- Initial versus re-validation

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Cleaning Validation

- The documents generated in relation to the cleaning validation study should be in compliance with the principles of good documentation practices and should meet data integrity requirements
- It is expected to have in place:
- CLEANING VALIDATION MASTER PLAN
- CLEANING VALIDATION PROTOCOL
- CLEANING VALIDATION REPORT
- APPROACH for MAINTAINING THE CLEANING VALIADTION STATUS
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