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Common Deficiencies Observed by Various Regulatory Agencies

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ABSTRACT

More than 50% of the total number of deficiencies related to the manufacturing sections of the Common Technical Document (CTD). Deficiencies related to API, Management of quality, Investigation of deviations, Corrective and preventive actions, Potential for contamination, Supplier and Contractor Audits, Design and Maintenance of equipment, Data integrity issues, Data manipulation, Manufacturing controls, etc., The number and pattern of deficiencies did not change over time. The most frequent critical deficiencies were related to the specific manufacturing process and the key materials used in particular the API starting materials, impact of the API impurity content.

Key-words: United State Food and Drug Administration (USFDA), Medicines and Healthcare products Regulatory Agency (MHRA), Active Pharmaceutical Ingredients (API), Common Technical Document (CTD), International Conference on Harmonization (ICH).

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Introduction

FDA believes that pharmaceutical quality system (PQS) element deficiencies are the major contributor to drug shortage. There was a huge reliance on just GMP compliance. Now with the introduction of ICH Q 10 we all have a much better understanding about Pharmaceutical quality system. Our main goal is to ensure patient safety, regulatory compliance and ultimately a successful business.

The root causes of Pharmaceutical Quality System deficiencies

1. Lack of understanding what an effective quality system includes.
2. Poor design and description of the quality system.
3. No common understanding across the company of what the quality system consists of and how it works.
4. No measures, or inappropriate measures, to indicate how well the quality system is working and driving the right behavior.
5. No regular formal senior management review of the quality system.
6. No formal system in place to drive continuous improvement of the quality system, led by the senior management team.
7. No formal system in place to drive continuous improvement of the products and processes.
8. Inadequate resources provided to monitor and improve the quality system.
9. A compliance culture rather than a quality culture.
10. No effective internal audit program to identify weaknesses in the quality system.

Perhaps these are the top 10 explanations as to why regulators still find GMP deficiencies, and why companies fail to meet current expectations. Essentially it indicates that most companies still have significant gaps in their pharmaceutical quality system and the individual components that make up the Pharmaceutical Quality system.

Deficiency database

The MHRA has been one of the few regulatory authorities to publish the statistics and classifications for the deficiencies that it finds during inspections. This is a great source of information and yet sadly does not appear to have had the desired effect of preventing further similar deficiencies. It is very clear that MHRA continues to have concerns about our quality systems. The last figures we have are for year 2013, and it is sincerely hoped that the MHRA continues to provide us with this invaluable lessons.

This is probably a misleading breakdown. It implies that quality management separate system from the others. In fact, each of these items is a key element of a pharmaceutical quality system and they all relate to how quality is managed.

In other words, it is all about how the Pharmaceutical quality system is designed, operated, monitored and improved. For example, the way that personnel are recruited, managed, trained, educated, informed, assessed and developed is probably the most important element of the Pharmaceutical quality system and yet it is a separate category in the MHRA listings. Without the right motivated people in the right jobs, given the right information to do their jobs well – none of the other systems will work. All the systems are interlinked and all form part of the Pharmaceutical quality system.

An essential characteristic of a Pharmaceutical quality system therefore is that all elements work together. Indicators that this is not happening are high levels of deviations previously assigned to human error. Such errors occur in the vast majority of cases because the Pharmaceutical quality system elements are not well designed and managed.

The major Pharmaceutical quality system Deficiencies

Essentially all deficiencies result from an ineffective Pharmaceutical Quality System no matter what heading you give it. Even deficiencies listed under categories 2 – 8 are symptomatic of the quality system not working effectively or not being designed, reviewed and improved as required by regulators.

Investigation of Deviations

An appropriate level of root cause analysis was not applied during the investigation of deviations and No formal documentation of the product impact assessment and associated rationale for determining whether issues encountered were significant deviations or lower level incidents. Regulatory expectations are that Deviation system must require all deviations to be classified or ranked based on risk to patient. Risk assessment must be documented. For those considered more serious, an effective impact assessment and root cause analysis must be

performed and documented. Appropriate corrections should be implemented and corrective action should be taken to ensure the problem does not reoccur. Internal audits should look for evidence of recurrence and deviations should be trended for the same purpose.

Quality Management

There was no self-inspection program established for the current year. There was no risk management procedure. Significant quality incidents were not included and Regulatory expectations are that senior management should ensure that the quality system includes all the necessary elements/systems that drive continuous improvement and risk-based thinking and should review them on a formal regular basis at a quality review meeting.

Corrective and preventive actions (CAPA)

It was unclear how CAPA actions were linked to the root cause. There was no process ensures CAPA actions from any system, including regulatory inspections, were completed on time and in full. There was no mechanism for measuring CAPA. Regulatory expectations are that all elements of the quality system can give rise to opportunities for improvement. CAPAs are by definition improvements, provided that they are effective. Any failures, complaints, deviations and audit findings should be prioritized based on risk and fed into the CAPA system. CAPAs must be implemented in a defined time frame and the effectiveness of the CAPA system must be monitored by various systems, e.g. internal audits, trending of deviations or other parameters, changes, CAPAs, etc.

Potential for contamination

There was no documented process for assessing the introduction of new molecules on the site. White powder was noted on a roller compactor that had been in the engineering workshop for six months. Unidentified white powder was noted on the production corridor floor and on a hand pallet truck. Regulatory expectations are that every company should have a documented approach to minimize contamination, including a requirement to raise a change request to introduce a new product or molecule, resulting in an impact and risk assessment. Effective design of facilities, equipment, and maintenance/cleaning programs should prevent product residue from causing a potential contamination of other products. Many elements of the quality system can contribute to contamination if not well designed and effective.

Supplier and contract audit

Audit report for a contract manufacturer was not available when site was added to approve supplier list. There was no contemporaneous evidence to base to approve manufacturer decision. Audit reports for an API were high level. It was not apparent what had actually been audited. Audit report for a supplier concluded the site was not suitable to supply an API due to GMP issues. API supplied had not been quarantined or rejected.

Regulatory expectations are that Supplier management system should not allow any supplier to be used without going through quality assessments. These assessments must be documented and available for inspectors to support the use of any supplier or contractor. If audits are required to form part of the assessment, the audit reports must be available and sufficiently detailed to support the use of the supplier. Any findings and recommendations made by the auditor should be addressed.

Premises

Unidirectional flow of man-material movement not in place, orientation of doors faulty with respect to positive pressure, uncleanable surfaces created by pipes, fixtures or ducts directly above products or manufacturing equipments, surfaces finish (floors, walls, ceilings)that do not permit effective cleaning, malfunction of the ventilation system resulting in possible migration of materials between manufacturing areas, accessory supplies(steam, air, nitrogen, dust collection ,etc..),Heating, Ventilation and Air Conditioner(HVAC) and purified water system not qualified ,temperature and humidity not controlled or monitored where required. Poor design and construction of premises is due to inadequate segregation, illogical process flow. Inadequate provisions for utilities is due to HVAC, water, compressed gases, Poor design and management of the HVAC system, multipurpose plant used re-circulated air but had no High Efficiency Particulate Air(HEPA) filters, Adequate pressure differentials: reversal of air flow. No sequence of switching on and off of Air handling units of adjacent areas.

Equipment's

Lack of qualification of critical equipment , faulty location, both for cleaning, air circulation, lack of maintenance to operate within its specifications, evidence of contamination by foreign materials such as grease oil and particles from the equipment. Status not defined, unused equipment improperly stored, Clean In Place (CIP) Equipment not validated. Inadequate facilities and equipment for handling potent hormone products, Inadequate containment from both a GMP standpoint BUT also safety and environmental perspective (which are present in the WHO guidance unlike other GMPs)

- Inadequate goods and materials management
- Starting materials: sourcing and sampling – ID per container.
- Packaging materials: inadequate sampling – ISO2859 or BS6001.
- Intermediate and bulk products – holding time not set, or justified, or respected.
- Finished products: Release procedures – no adequate review by QA or QP.
- Rejected materials and products: not adequate segregation or disposal.
- Reagents and culture media: no GPT, positive and negative control
- Reference Standards: inadequate standardization, storage and use

Validation

Non-risk based validation leading to a failure to concentrate on risks and doing non-value added validation by rote!

- Poor practices for usage and cleaning accepted as covered & justified by "passing" results of manual cleaning or residue testing!
- Good history does not mean failures do need not be investigated sometimes incomplete validation of content uniformity and blending due to sample size taken, poor cleaning practice, unvalidated cleaning
- Heavy use of manual cleaning techniques which are difficult if not impossible to validate
- Risks from machine lubricants
- Long campaigns during which contamination accumulates

- The most frequently found deficiencies were: Material management, Standard Operating procedures, cleaning
- Others included: Batch records, labeling, cross contamination

WHO GMP for APIs: Buildings, utilities and equipment

- Precautions implemented based on a risk assessment
- Utilities (HVAC, compressed air and other gases etc) qualified and monitored, as appropriate.
- Buildings and equipment cleaning methodology and intervals appropriate to–Facilities designed to prevent mix-ups and contamination prevent build-up and carry-over of contaminants (degradants)
- Facilities, equipment and utilities system

CRO Inspections: Inadequate data integrity Source data either not available or authenticity questionable:

- Source data could not be located to verify entries in Virtual Routing and forwarding (VRF)
- Destroyed accidently by fire or rain
- Sponsor claims the data were kept by the Contract Research Organization (CRO), and the CRO claims the data were kept by the sponsor
- Two of the ECGs shown to the inspectors, bearing different subject numbers and initials, were found to be identical.
- Other ECGs bearing different subject numbers and initials appear to have been recorded from a single subject. Out of 95 ECGs copied by the inspectors, 43 appear to have been recorded from the same and single subject during a single session

Data manipulation – inappropriate manual integration of peaks

- Manual reintegration of peak was done inappropriately and inconsistently for all peaks inclusive internal standard, for some samples checked, especially QCs or standards close or outside the 15% of

their nominal concentration, the baseline of the chromatograms were modified manually. This was not done appropriately and consistently for all peaks inclusive internal standard. For modified integration, initial integration was not available.

- No paper or electronic audit trail of manual integration available.
- Each analytical run did not include calibration and quality control samples.

Personnel

Job descriptions, job responsibilities not well defined. Overlapping of functional areas. Lack of effective training and its evaluation on induction and periodically contract labors involved in manufacturing areas inadequate self contained suits for workers in hormonal areas. Significant importance of personnel undermined. With respect to premises, production, processes, procedures

Sanitation

No or incomplete health and hygiene program, not properly implemented or followed by employees, Employees are not subjected to test for sensitivity towards potent drugs on site, incomplete records on the application of the sanitation program, personnel responsible for the application of the cleaning procedures not identified, sanitation programs are not followed, accumulations of residues-cobwebs found.

Manufacturing Controls

Lack of proper identification of in-process materials and production rooms resulting in a high probability of mix-ups., improper quarantine and disposal practice, insufficient process and cleaning validation, absence of or non-validated changeover procedures, master formula incomplete or showing inaccuracies in processing operations and not updated/reviewed, inadequate inaccurate labeling of bulk or in-process drugs, raw materials, product materials, Absence of a validated process for changes in batch size or combination of batches., Absence or incomplete SOPs for handling of materials and products, Incomplete validation studies reports for critical processes(lack of evaluation approval),unapproved undocumented major changes compared to master production documents, deviations from instructions not documented or no final approval from Quality Control ,discrepancies in yield or reconciliation following manufacturing and packaging not investigated

Sampling not performed as per the defined Standard Operating Procedure(SOP) and plan. Falsification or misrepresentation of analytical results, not tested to ensure compliance with their specifications, incompletely addressed of storage, handling, stability and not followed where specified, Deviations of receipts, from unapproved vendors, No system for notification of changes in specifications and process by the vendor.

Quality control department

Inadequate facilities, personnel and testing equipment, Instruments are not recalibrated after a repair or replacement of part, change control are not addressed when changes in specification methods or any part of it, improper documentation, Deviations in written procedures are not documented, lacked a comprehensive sop for different activities of micro lab like plate pouring, colonies counting, aseptic techniques, media preparations, serial dilutions, computerized system-data manipulation**.**

Data integrity issues

- Shortage of manpower: Shortage of staff and executive work, pressure can lead to inaccurate and incomplete documentation.
- Quantity over Quality: Employees may be forced to compromise the acceptable quality levels in order to meet production targets or dispatch timelines.
- Lack of awareness: often employees are not trained or inadequately trained to understand GMPs. This causes employees to consider activities as a chore rather than understanding their importance in light of GMPs.
- Effectiveness of trainings: Company may hire the best international trainers, employees mentioned that there were language barriers, which prevented the employees from understanding the contents, thereby making the training effective.
- Non contemporaneous recordings: failure to record activities at the time when activity has performed. There is evidence that the records were signed by company personnel when the person was actually

absent on that day.

- Document back dating: Backdating stability test results to meet the required commitments.
- Copy of existing data as new information: test results from previous batches were used to substitute testing for another batch or acceptable test results were created without performing the test.
- Rerunning samples to obtain better results: Multiple analyses of assay were done with the same sample without adequate justification and in some cases sample were tested unofficially or as a trial analysis until desired test results obtained.
- Data fabrication and data discarding: Original raw data and records were altered for e.g., by using of correction fluid or Manipulation of a poorly defined analytical procedure and associated data analysis in order to obtain passing results.

Poorly designed processes:

- Materials transferred between unit processes with inadequate assurance of integrity and contamination risks. Inadequate dust extraction and containment, Excessive holding times for intermediates those are unvalidated.
- Raw material suppliers not audited but acceptance of side samples accepted with no justification.
- No understanding of ingredient variability and its effect on packaged product.
- Container suppliers and packaging material suppliers never audited.
- Poorly designed or maintained equipment:
- Equipment not easy to clean especially dust extracts.
- No traps in dust extract systems.
- Unvalidated cleaning and reuse of filters.
- Inappropriate filter grades for material handled.
- Poor control over metal items-inparticular sieves.
- Construction activities.
- Major constructions in room next to personnel entry airlock (eg.gowning)
- Construction occurred approximately one month period and coincided with continued production.

Stability

Stability chambers are not provided as per product requirements, No records of monitoring and no provisions of data and power back ups, Insufficient number of lots, insufficient data to establish shelf life, No stability studies prior to changes in manufacturing (formulation) or packaging materials, Falsification or misrepresentation of stability data, No actions on data where deviations trend analysis of the results before its expiry.

Sterile products

Sterility assurance is not satisfactory established in case of Aseptic practices, sterilization, process design, media fill ,sterility investigations ,critical sterilization cycles not validated, WFI systems are not validated, No or insufficient media fill performed to demonstrate the validity of aseptic filling operations, Environmental monitoring: inadequate sampling methods .Inadequate training of personnel/training requirements, sanitation/disinfection programmed incomplete, Inadequate SOP; practices and precautions for minimizing mix-ups .Non-validated time interval between cleaning, sterilization, use of containers, components and equipments, samples for sterility not representative of the entire production.

ICH Q10 management commitment

Senior management has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the quality objectives and that the roles, responsibilities and the authority defines, communicated and implemented throughout the company. Leadership is essential to establish and maintain a companywide commitment to quality and for the Performance of the pharmaceutical quality.

Designing of GMP compliant facility

- Air Handling Unit (AHU) is necessary for GMP.
- Rest and refreshment rooms are separate from manufacturing and quality control areas.

- Canteen separate areas.
- Materials and products are protected from weather.
- Separate sampling areas so that no risk of contamination or cross-contamination.
- Segregated areas for rejected, recalled or returned materials and products.
- Safe and secure areas for highly active, radioactive materials, narcotics and other materials(risk of abuse, fire, explosion)
- Online area monitoring with alarm system like security gate alarm or email or sms for immediate alert.
- A minimum of 10-15 pascals should be maintained between the aseptic area and an adjacent rooms with differing clean room classifications(door open)
- Protection from insects, birds vermin and weather
- Interior surfaces (walls, floors, and ceilings)-smooth, free from cracks and open joints.
- All drain traps should be cleaned and sanitized on a regular basis.
- Drain traps and covers should be in place and in good repair.

Conclusion

As time passes compliance level also increase, so that deficiencies level is decreased. Regulators are always do their duty very well. Perhaps it is a poor indication of any company if it waits for regulators to force it to improve..!! Continuous improvement, driven by the senior management team, is essential for any company to stay in business and of course it is a legal requirement in GMP and an essential component of a Pharmaceutical Quality System. Regulator want to see companies taking the initiatives and in particular senior management do the continuous quality improvement, which is a good business sense anyway, that is a key difference between quality culture and quality.

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