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How to build an effective pharmaceutical quality system

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How to Build an Effective Pharmaceutical Quality System

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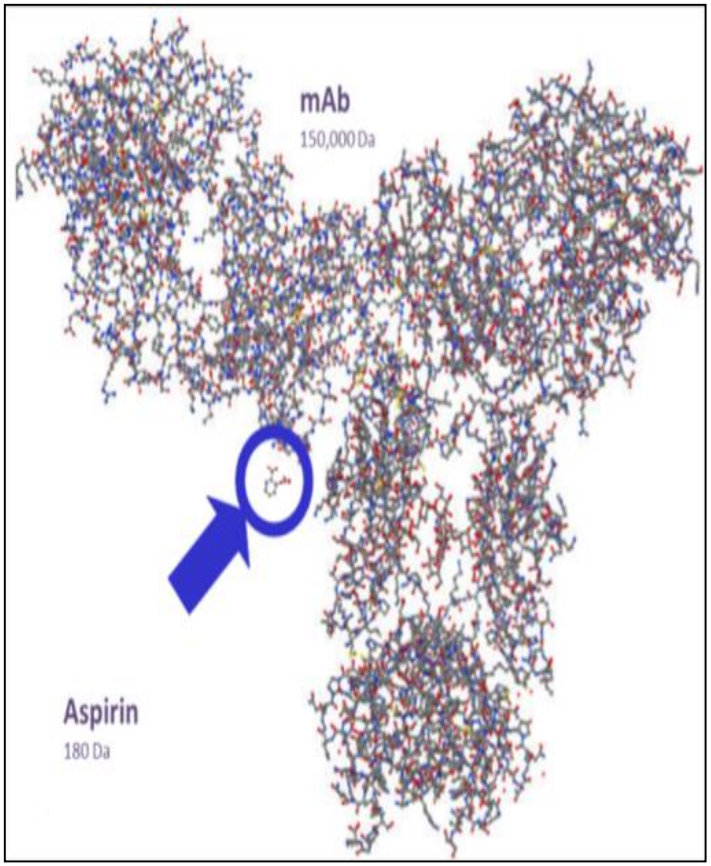
Biological products (BP)

- Biological products can be defined according to their source material and method of manufacture
- Biological products are derived from cells, tissues or microorganisms
  - Vaccines
  - Animal immune sera
  - Monoclonal antibodies
  - ATMPs
  - Cytokines
  - Product of fermentation
  - ….

Ref: WHO TRS 996, 2016 GMP for Biological Products section 1

Biologicals versus chemicals

- Biologicals are often too complex to be fully characterized by physicochemical testing methods alone
  - Require In-vivo testing (using animals)
- More fragile, thermolabile
  - Require Storage at low temperatures
- High risk of viral, BSE/TSE contamination
- Complex impurities profiles
  - Biological residues
  - By process residues



Biologicals versus chemicals

- Biological processes are prone to microbial growth
  - Products, process intermediates and raw materials support microbial growth (e.g., buffers, column resins, filtration membranes, processing conditions are favorable to bio-burden growth and biofilm formation)
- Cell culture processes are also susceptible to adventitious contamination
- Bio-burden can increase endotoxin levels
- Contamination of biological products and intermediates can lead to degradation, loss of potency, immunogenicity, heterogeneity, change impurity profiles and, ultimately, inconsistent processes.

Background

- Biopharmaceutical companies are under pressure to both innovate and successfully manage increasingly complex operations and current regulatory requirements;
- The obvious question comes to mind, do we need to redesign the quality management system (QMS) to ensure a lean and agile QMS without increasing quality-related costs;
- An effective QMS facilitates innovation and continual improvement, and also strengthens the link between pharmaceutical development and manufacturing activities;
- A Streamlined structure ~~that~~ enables both compliance and operational efficiency;
- Flexibility to incorporate different modalities easily;
- Misalignment between the QMS and operational requirements may have downsides and drive costs.

What is expected?

- BP, like any pharmaceutical product, need to be manufactured in accordance with pharmaceutical quality system (PQS) requirements as defined in WHO GMP;
- QRM principles need to be used to develop control strategy across all manufacturing and control stages – including materials sourcing and storage, personnel and materials flow, manufacture and packaging, quality control, quality assurance, storage and distribution activities;
- Due to inherent variability of biological processes and starting materials, ongoing trend analysis and periodic review are particularly important elements of PQS;
- Special attention needs to be paid to starting material controls, change control, trend analysis and deviation management in order to ensure production consistency;
- Monitoring systems need to be designed so as to provide early detection of any unwanted or unanticipated factors;
- Effectiveness of control strategy in monitoring, reducing and managing such risks needs to be regularly reviewed and systems updated.

How this can be achieved?

- ICH Q10: Pharmaceutical Quality System - 2008
- A comprehensive approach to an effective pharmaceutical quality system that is based on ISO concepts, includes applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q8 "Pharmaceutical Development" and ICH Q9 "Quality Risk Management"
- A harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science.
- ICH Q10 aims to promote a paradigm shift from discrete GMP compliance procedures at each stage of the product lifecycle to a comprehensive quality systems approach over the lifecycle of the product.

How this can be achieved?-2

- ICH Q10: The objectives are to:
  - Achieve product realization
  - Establish and maintain a state of control
  - Facilitate continual improvement
- The ICH Q10 applies throughout the product lifecycle, including:
  - Pharmaceutical development
  - Technology transfer
  - Commercial manufacturing
  - Product discontinuation
- ICH Q10 augments GMP which are generally not repeated within the (Q10) Guideline

Managing Knowledge

- Manufacturer is required to formally acquire, analyze, store, and disseminate product and process knowledge throughout product life-cycle.
- These processes help to ensure effective product development, scale up, technology transfer, process validation, continual improvement and post-approval change management that meet applicable regulatory and manufacturer requirements.
- Managing knowledge, including:
  - Out of specifications: may indicate a flaw in product or process design
  - Deviations: lack of robustness in product formulation
  - Process failures: substantial variation introduced by one or more unit operations
- In such cases, it is essential that redesign of the product or process be undertaken to ensure reproducible product quality.

Quality Risk Management (QRM)

- **Effective and proactive QRM can facilitate better & more informed decisions;**
- **QRM provides greater assurance of manufacturer's ability to foresee and avoid potential crisis;**
- **Examples to illustrate importance of effective QRM for shared facility, include:**
  - **Identifying and mitigating various risks involved in manufacturing of different vaccines**
  - **Mapping of various process steps starting from receipt to packing of finished product**
  - **Evaluating each process step to identify current control measures and associated risk involved**
  - **Pre-assessment, including risk identification during mechanical transfer, airborne transfer, product mix-up, retention/residue**
  - **Assessment, including use of tools such as FMEA to identify potential failures and mitigation plan**
  - **Post assessment, including risk mitigation and ongoing monitoring**

Examples of inspection findings

1. The company has not implemented and maintained a robust and well-resourced QMS:

- Change controls not fully implemented
- Performance and review of product quality review deficient
- No policy or procedure on the assurance of data integrity including management oversight

2. PQS in place, but was not considered adequate, consistent, robust, reliable and in compliance with GMP standards.

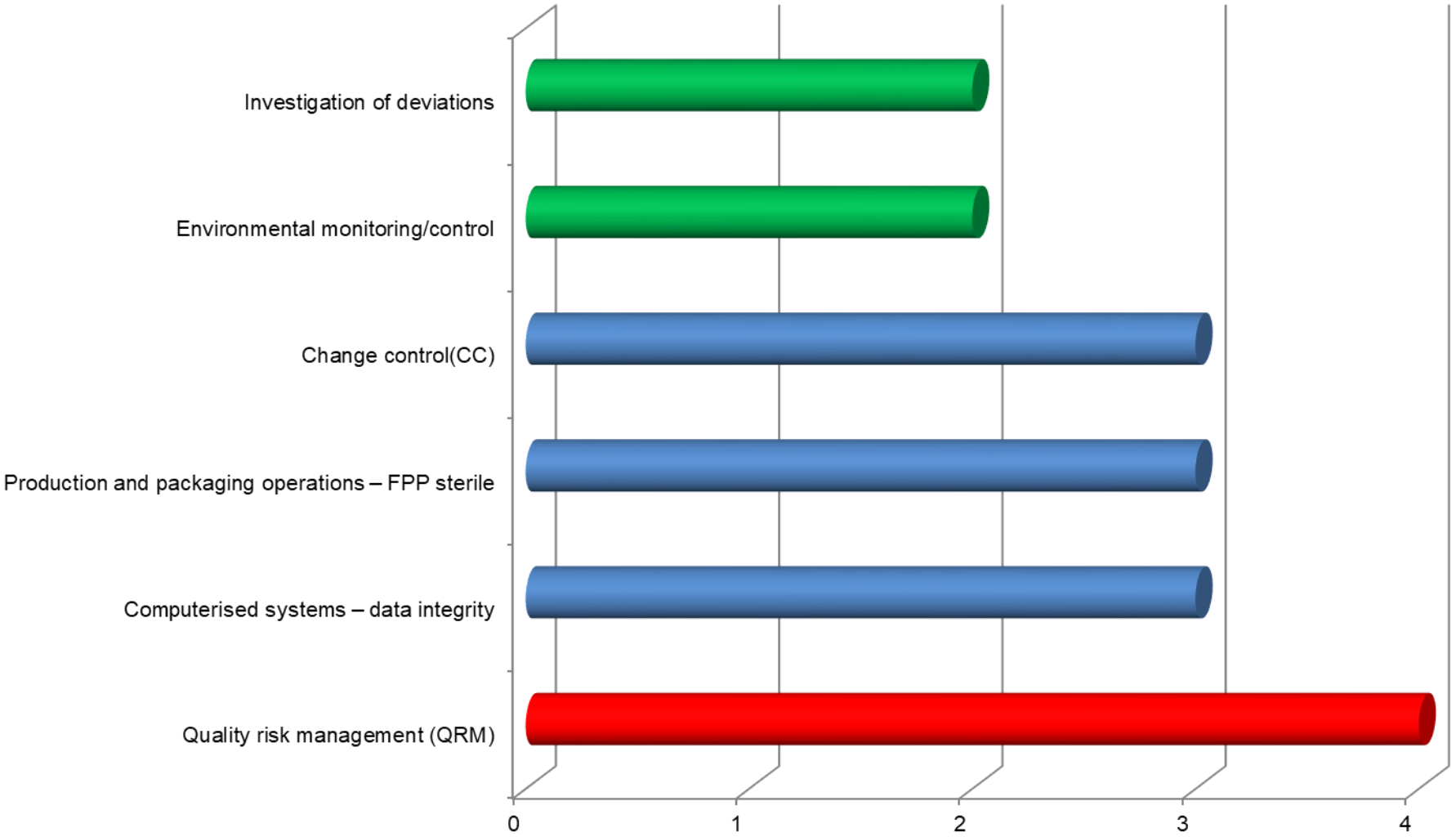
- Existing quality system could jeopardize product quality and patients´ safety.
- Senior management is not ensuring that the products manufactured are fit for their intended use, comply with the requirements of the Marketing Authorization and do not place patients at risk due to inadequate safety, quality or efficacy.

Examples of inspection findings

The company approach to QRM was deficient. The QRM programme was not adequately developed and implemented in a comprehensive manner.

Seven persons were working in vial cap sealing room which was classified as Grade A/C. Frequently rubber stoppers were bumping up on conveyer before sealing process thereby causing generation of powder particles and exposing sterile product to grade A/C before completion of sealing process. This incident of accidental cross-contamination was not justified with adequate risk assessment.

Sterile FPP Major deficiencies 2017



GOLDEN RULES

1. Build good premises
2. Equip your premises with suitable equipment / machinery
3. Maintain buildings and equipment in a proper manner.
4. Write standard operating procedures (SOPs)
5. Validate your procedures and working practices
6. Train your personnel in cGMP
7. Record your work: ALCOA
8. Be clean in all things you do
9. Test for quality not for compliance
10. Internal audits for compliance

A robust quality system will ensure these ideals are achieved.

Concluding Messages-1

- ✓ Quality objectives should be clearly linked to business objectives and strategy
- ✓ The QMS should be easily understandable, and should clearly establish the link between quality policy and ground-level execution
- ✓ Sufficient flexibility within the system is needed to incorporate site-specific nuances and enable continuous improvement
- ✓ To readily adapt to regulatory changes, the system should be dynamic and have sufficient controls

Concluding Messages-2

- ✓ QMS needs to be pragmatic, balancing compliance risk with simple-to-use and simple-to-understand processes
- ✓ Company to ensure all elements of QMS are well connected and work together effectively e.g.
- ✓ "Outsourced" activities e.g. contracting of testing when relevant equipment/technology not available on site and use of contract manufacturing organization for certain unit operations
- ✓ Process improvements - Is process knowledge used for improvement?
- ✓ An effective proactive quality risk management process
- ✓ Internal audits / self inspections
- ✓ Product Quality review