Promoting the Quality of Medicines

Welcome

USP U.S. Pharmacopeial Convention

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Promoting the Quality of Medicines

GMP Requirements

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Outline

- GMP
- Procedures and standards used for WHO Prequalification (PQ) inspections
- Observed deficiencies during Inspections
- Common Manufacturers Deficiencies (PQM experience)

What is GMP?

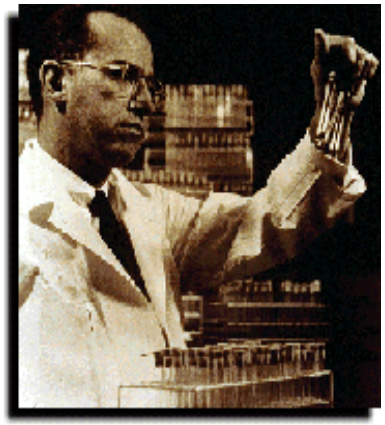
- **“**GMP” ensures the quality of drugs, medical devices, blood, and some types of food. The regulations cover manufacturing, facilities and controls for the manufacturing, processing, packaging or holding of a drug product.
- These were a response to concerns about substandard drug manufacturing practices occurring in the past.
- GMP refers to the Good Manufacturing Practice Guides published by the WHO/EU/PIC/S or Regulations published by the FDA under the Federal Food, Drug, and Cosmetic Act.

Why GMP?

History of poor manufacturing techniques resulted in deaths and injuries.

A consumer usually cannot detect (through smell, touch, or sight) that a drug product is safe or if it will work.

Testing alone is not adequate to ensure quality.

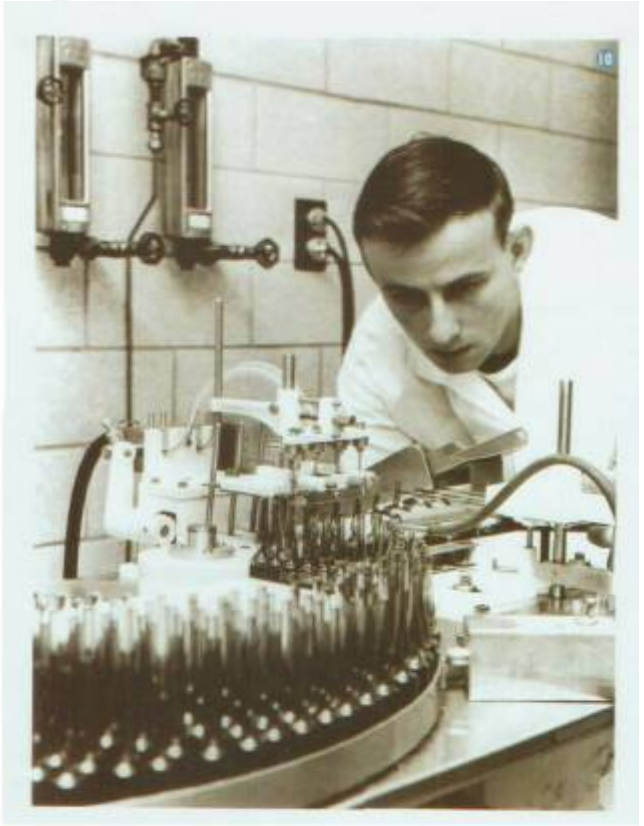


Photos – March of Dimes

cGMP

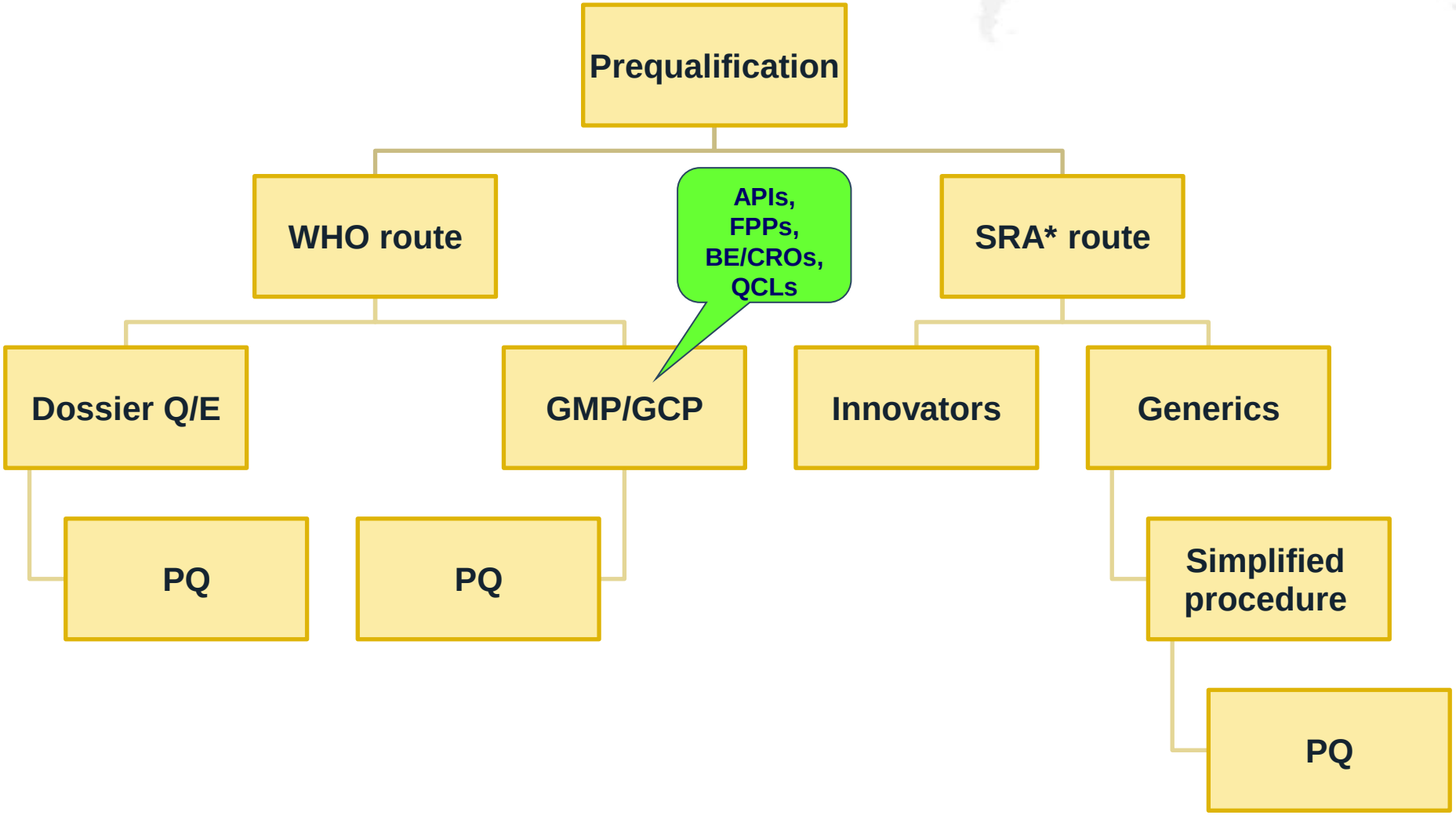
- cGMP requirements are flexible to allow each manufacturer to decide how to best implement the necessary controls using scientifically sound design, processing methods, and testing procedures.

- Flexibility allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement.



Operator adjusts machine that automatically fills and heat seals ampuls, 1957. *Courtesy of the American Institute of the History of Pharmacy*

WHO Prequalification: Inspection Activities



*Stringent Regulatory Authority

Overview of Inspection Activities

Planning and scheduling audit

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Conducting document review

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Preparing for on-site activities

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Conducting audit

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Prepare inspection report

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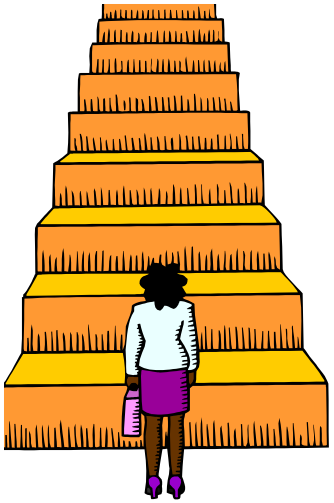
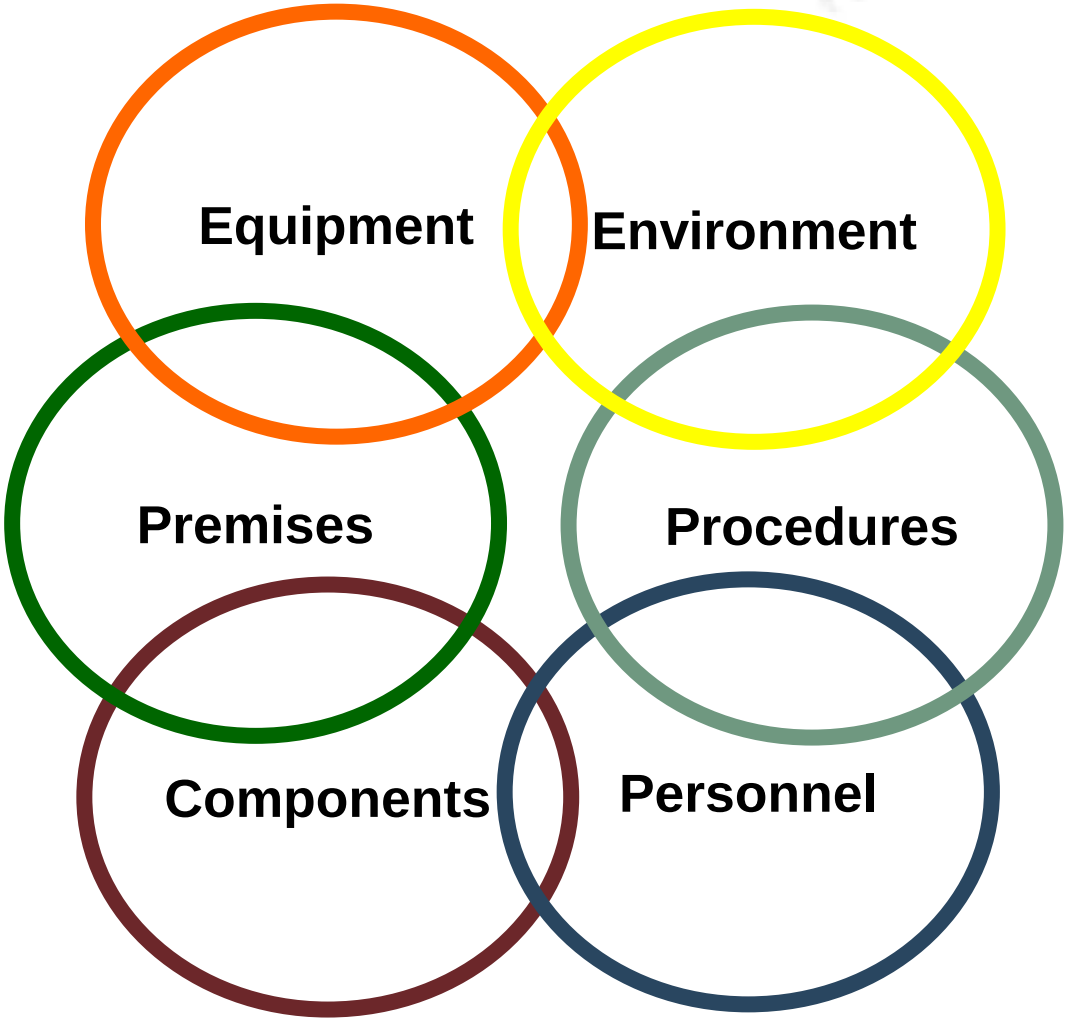
Conducting follow-up



Prequalification: Inspection Processes

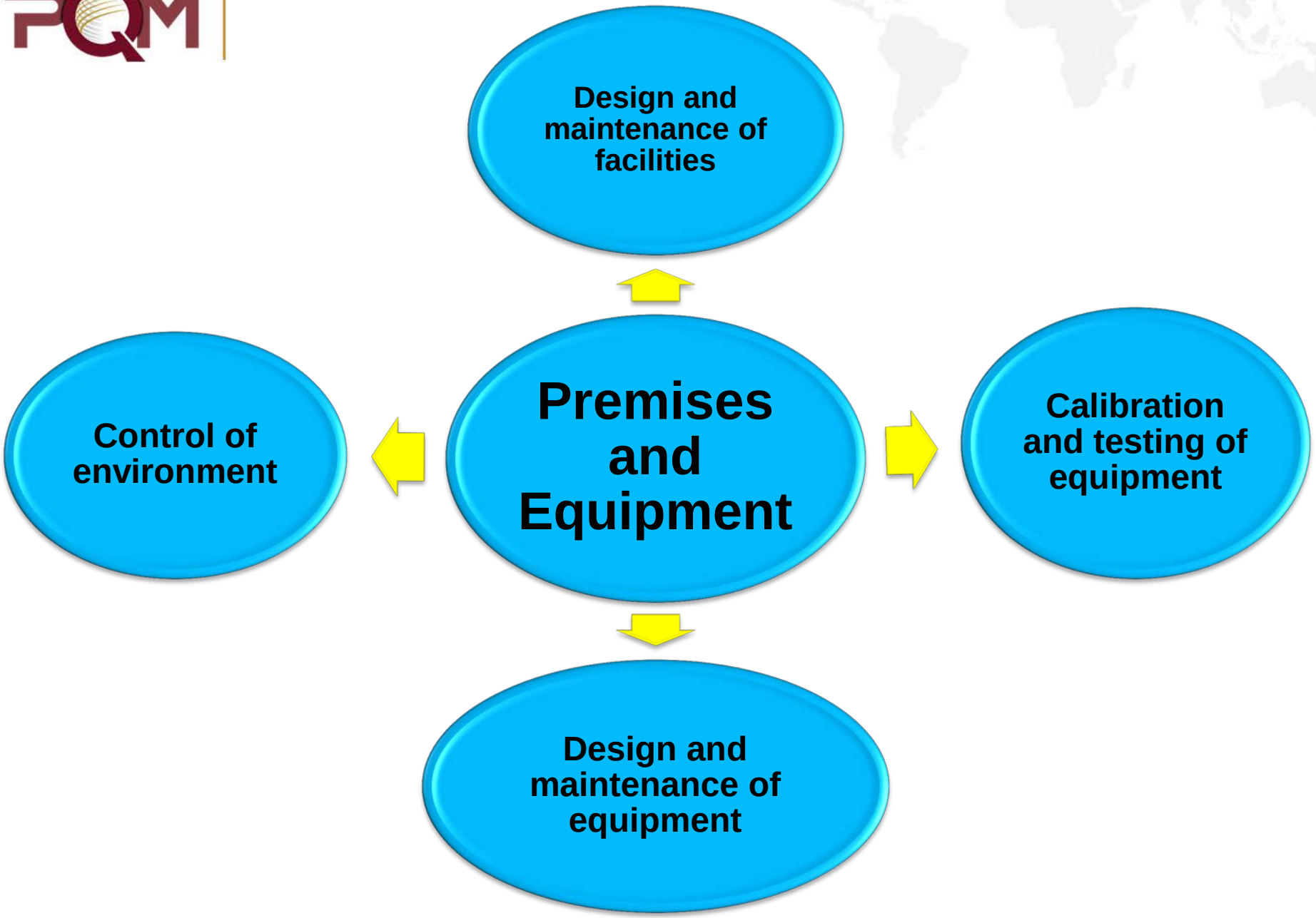
- Scope:
  - Compliance with guidelines:
    - GMP for API and FPP sites
    - GCP for CROs
    - GLP for FPP/API factory
  - Compliance with the dossier and commitments:
    - Data verification – data manipulation, falsification, (validation, stability, clinical, bioanalytical)

Factors for Quality Products



Basic Requirements for GMP

1. Clearly defined and systematically reviewed processes
2. Critical steps validated
3. Appropriate resources: personnel, buildings, equipment, materials
4. Clearly written procedures
5. Trained operators
6. Complete records, failure investigations
7. Proper storage and distribution
8. Recall system
9. Complaint handling



WHO GMP: Main Principles

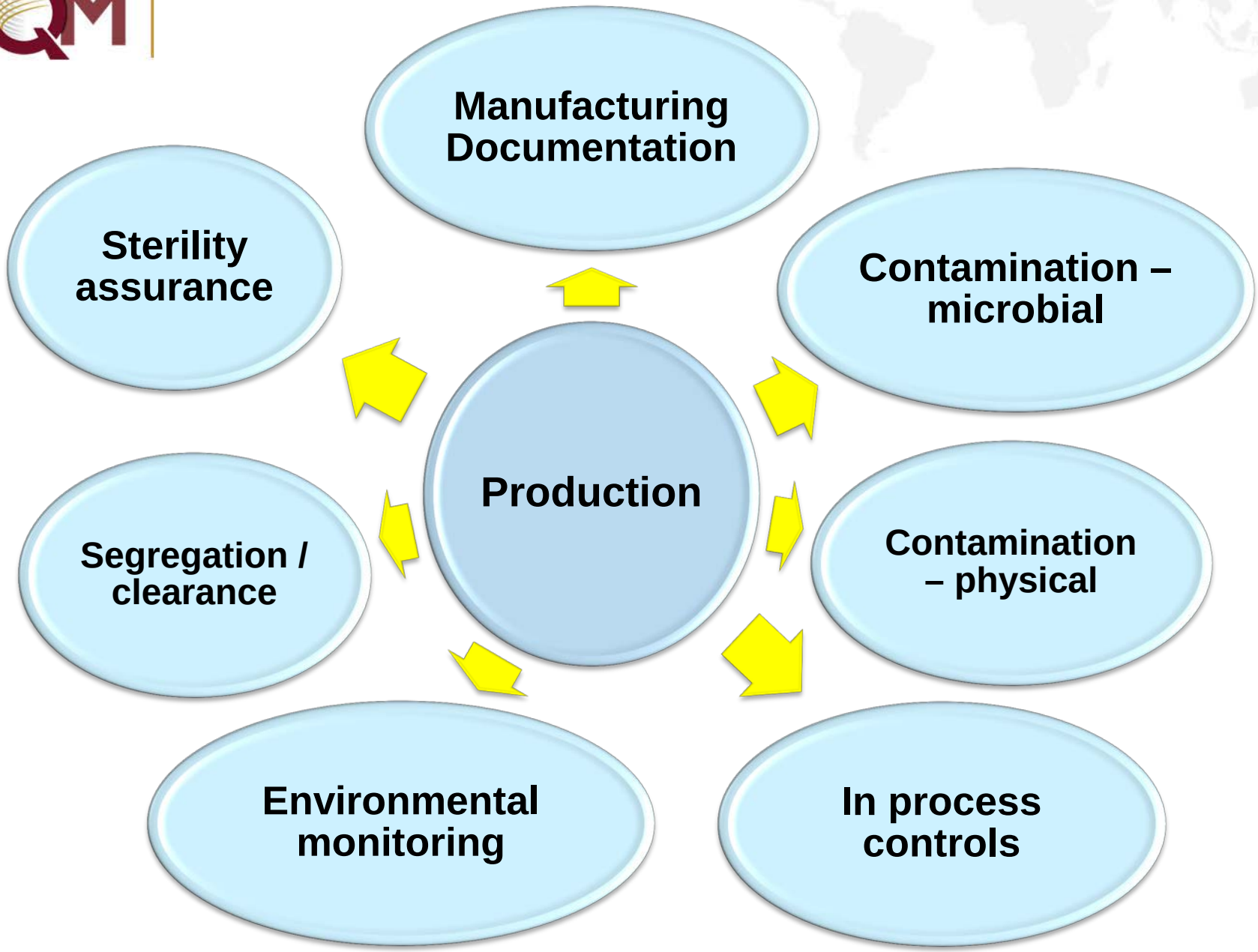
Premises

Design and construction of premises:

- Adequate segregation
- Logical process flow
- Adequate provision for Utilities: HVAC, water, compressed gases

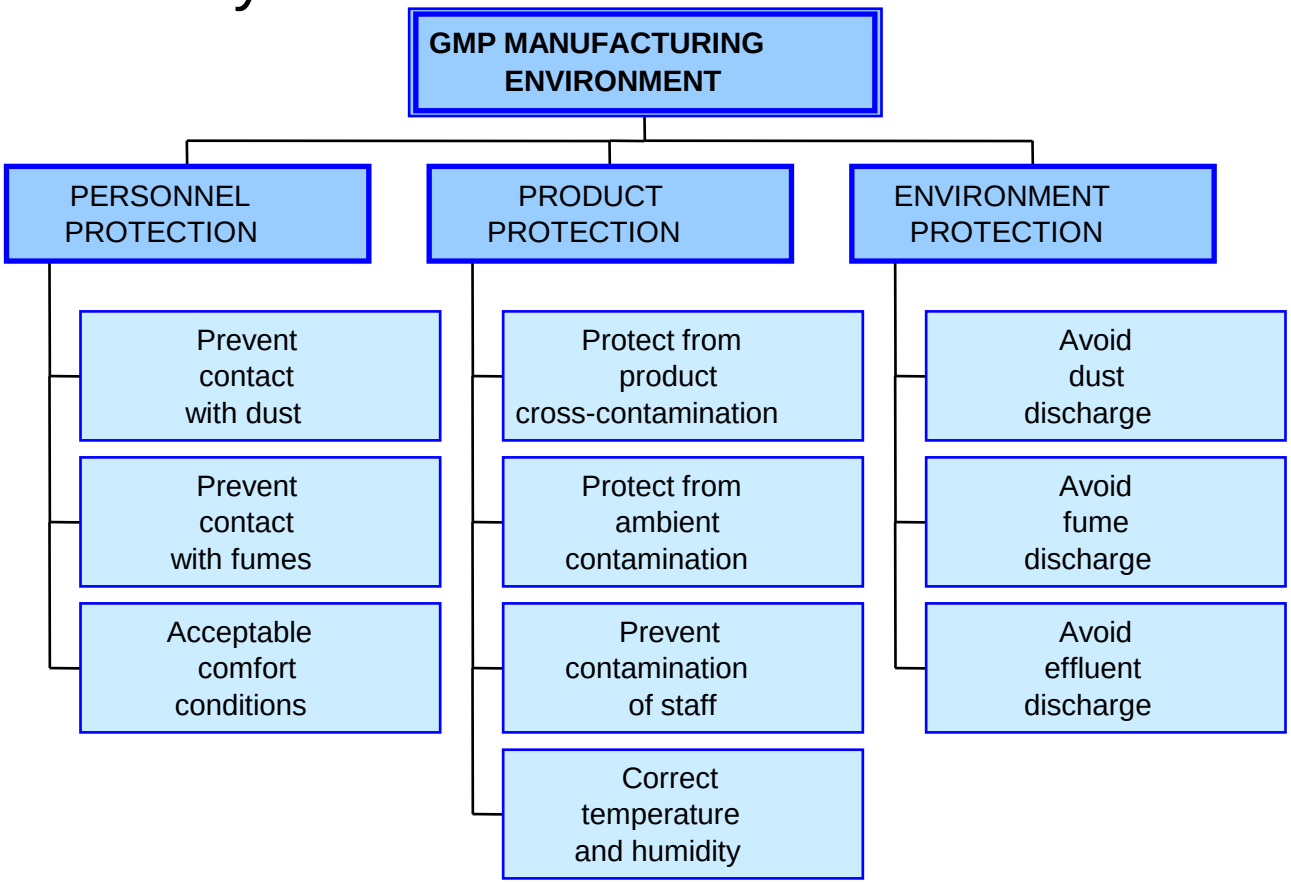
Design and management of the dust control and HVAC system:

- Contain dust at point of generation
- Effective air filtration (HEPA) in multipurpose plant with re-circulated air
- Adequate pressure differentials: avoid reversal of air flow
- Sequence of switching on and off of AHUs of adjacent areas



Design Considerations: Manufacturing Facility

- Three primary considerations to be addressed to ensure a safe and productive manufacturing facility



Source: WHO

What are Contaminants?

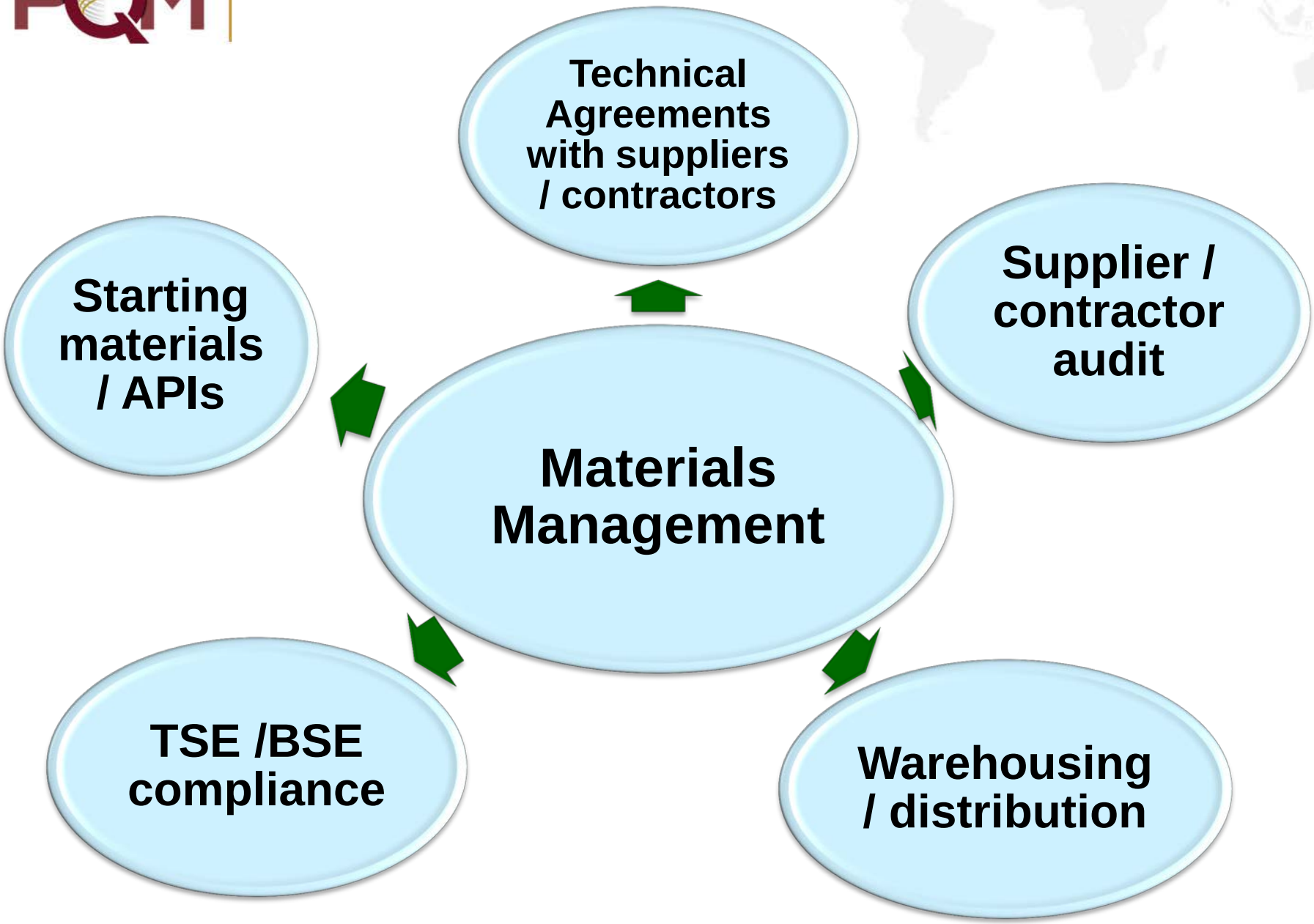
Contaminants are :

- Products or substances other than product manufactured
- Foreign products
- Particulate matter
- Micro-organisms

- Cross-contamination is a particular case of contamination “Contamination of a starting material, or of a product with another starting material or product.”

Source: WHO Photo credit: David Buckley

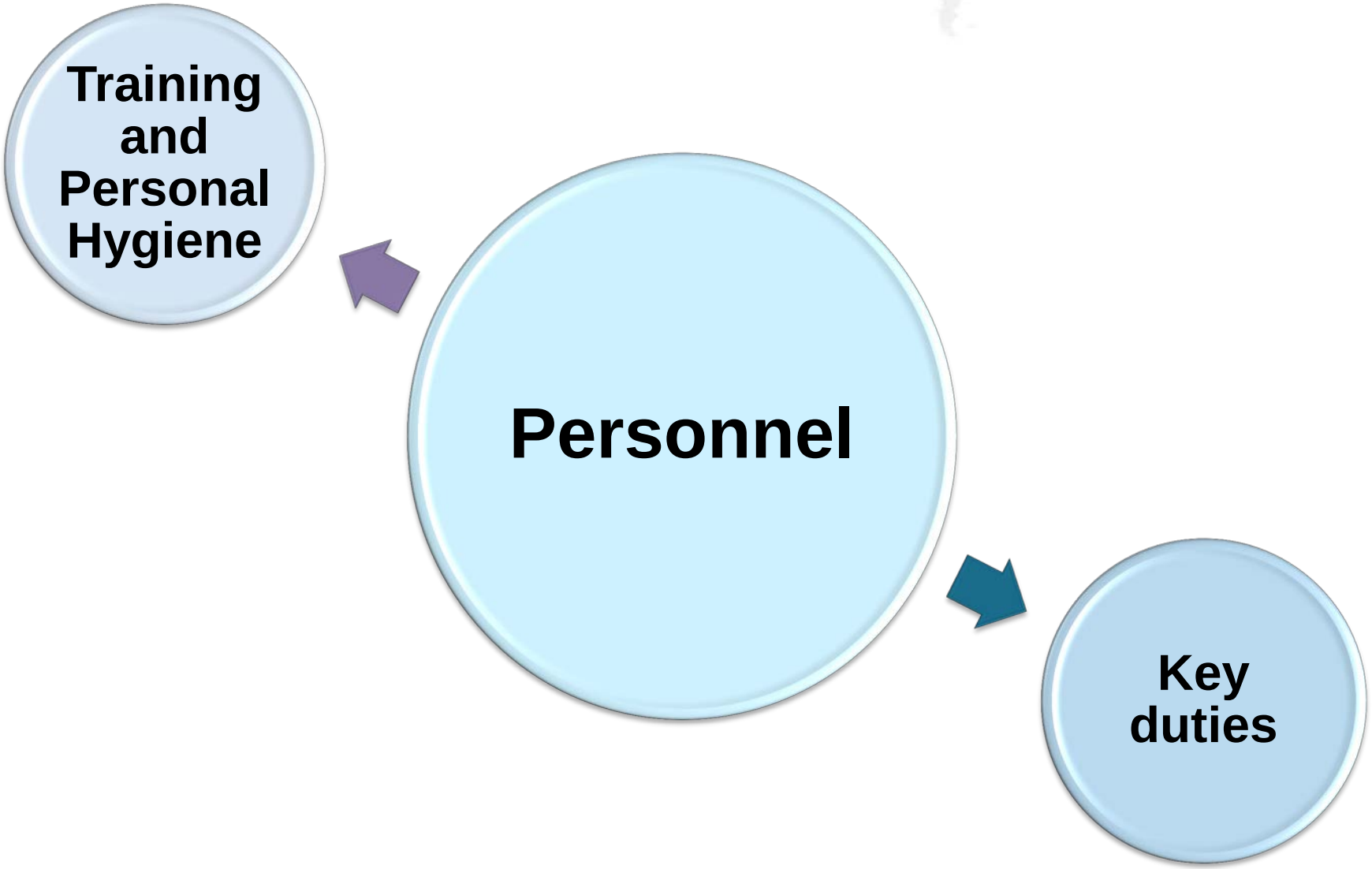
Photo credit: David Buckley



WHO GMP: Main Principles

Materials

- Goods and materials management:
  - Starting materials: Sourcing and sampling – ID per container
  - Packaging materials: Adequate sampling
  - Intermediate and bulk products – Holding time set, justified and respected
  - Finished products: Release procedures – Adequate review by QA or QP – all deviations reviewed and closed
  - Rejected materials and products: Adequate segregation or disposal
  - Reagents and culture media: Growth Promotion Test (GPT), positive and negative control
  - Reference Standards: Adequate standardisation, storage and use



WHO GMP: Main Principles for Pharmaceutical Products

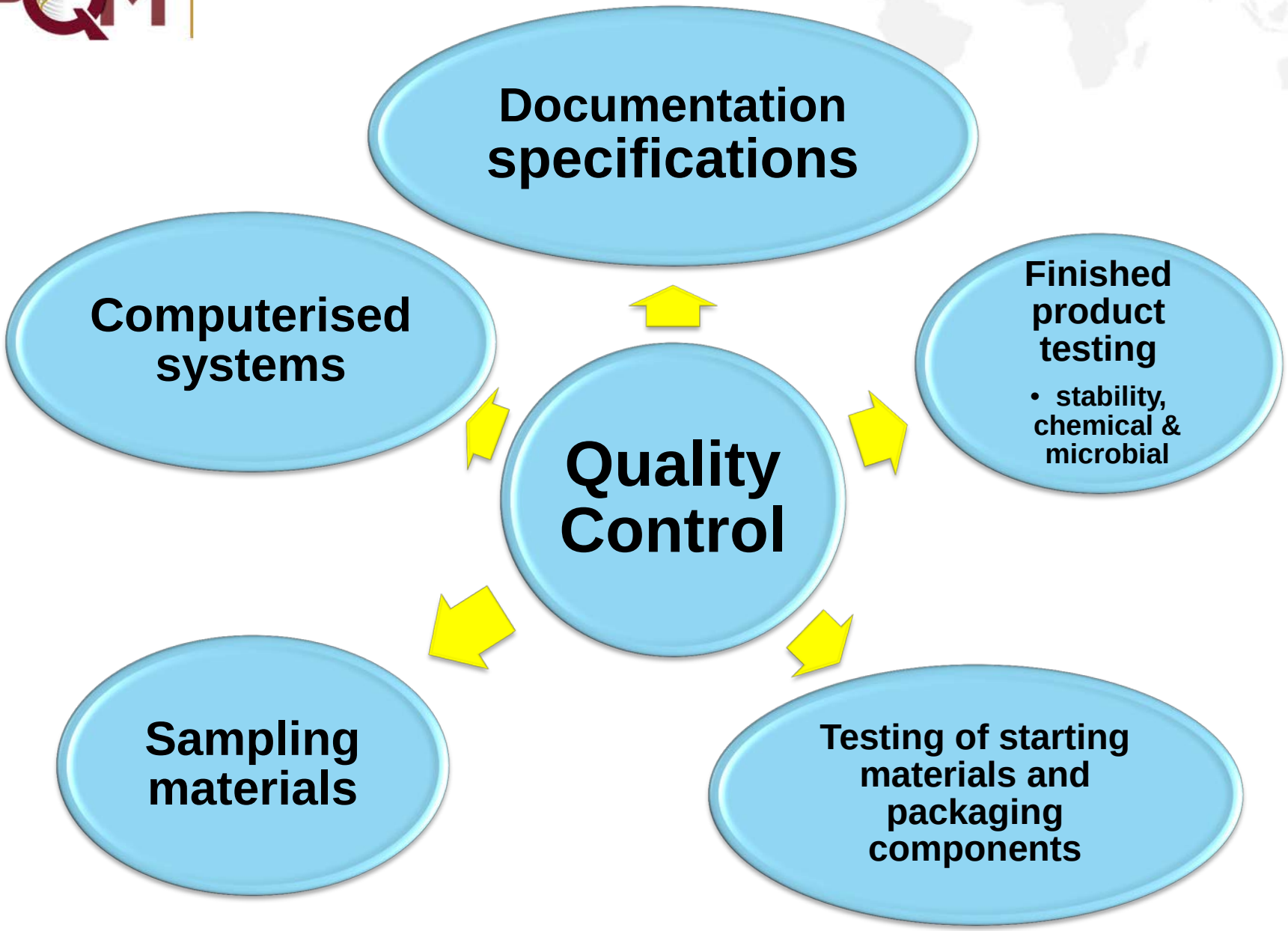
Personnel

- Personal Hygiene:
  - Medical examination prior to and during employment
  - Eye examination for visual inspectors
  - Personal hygiene training
  - Protective wear
  - Reporting apparent illness or open lesions

- Training:
  - Adequate staff with skills for assigned roles
  - Training: on recruitment, continuing training,
  - Training records
  - Practical effectiveness of training periodically assessed

Requirements for QA Systems

1. Ensure products are developed correctly
2. Identify managerial responsibilities
3. Provide SOPs for production and control
4. Organize supply and use of correct starting materials
5. Define controls for all stages of manufacture and packaging.
6. Ensure finished product correctly processed and checked before release
7. Ensure products are released after review by authorized person
8. Provide storage and distribution
9. Organize self-inspection



WHO GMP: Main Principles

Qualification, Calibration and Validation:

- Qualification: Equipment and systems (HVAC, Water, etc.)
- Calibration: Should cover the working range
- Process validation: Evidence of consistency–data integrity

Product Recalls

- Effectiveness of recall procedures assessed and regularly evaluated – mock recall
- Notification of authorities and clients:
  - DRA of the country, overseas customers, or DRAs notified

Contract Production and Analysis

- Contract acceptors evaluated before awarding them contracts
- Responsibilities of contract giver and receiver clearly defined

WHO Deficiencies: API Sites

Top 10 Areas for Improvements: 2014

1. Design, Maintenance and Cleaning of Equipment
2. Product Quality Review (PQR)
3. Process Validation
4. Computerized Systems – data integrity
5. Change Controls
6. Production and Packaging Operations
7. Design, Maintenance & Cleaning of Production Premises
8. Documentation Control
9. Investigation of out of specification (OOS), Deviations
10. Quality Risk Management

WHO Deficiencies: FPP Sites

Top 10 Areas for Improvements: 2014

1. Product Quality Review (PQR)
2. Design, Maintenance and Cleaning of Equipment
3. Computerized Systems – data Integrity
4. Contamination & Cross Contamination (physical/chemical)
5. Investigations of Deviations, out of specification (OOS)
6. Contamination & Cross Contamination (microbial)
7. Change Controls
8. Design & Maintenance of HVAC system
9. Design, Maintenance & Cleaning of Production Premises
10. Documentation Control

UK MHRA Deficiencies 2014

Comparison of top 10 most cited deficiency groups between 2016 and 2015

	2016	2015
Ranking	Groups	Groups
1	Quality System	Quality System
2	Sterility Assurance	Complaints and Recall
3	Production	Documentation
4	Complaints and Recall	Quality Control
5	Qualification/Validation	Computerised Systems
6	Premises & Equipment	Production
7	Computerised Systems	Premises & Equipment
8	Personnel	Validation
9	Documentation	Personnel
10	Quality Control	Materials Management

Source: https://mhrainspectorate.blog.gov.uk/2017/04/21/2016-gmp-inspection-deficiency-data-trend/

FDA Warning Letters Typical Headings

- Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data
- Failure to investigate and document out-of-specification results
- Failure to include adequate documentation during complaint investigation
- Failure to maintain complete data derived from all testing and to ensure compliance with established API specifications and expectations pertaining to data retention
- Failure of your quality unit to ensure that materials are appropriately tested and the results are reported
- Failure to ensure reprocessing procedures consistently yield API meeting its intended specification
- Failure to record activities at the time they are performed

Common Manufacturers Deficiencies - PQM Experience

Design and Maintenance of Premises

- Use of low quality building materials leading to easily damaged walls and doors which become difficult to clean
- Incorrect airflows and pressure differentials to prevent cross-contamination
- There was no de-duster and metal detector for compression machines
- The blender seal was in poor condition and staff had been using sealing tape to contain leakage
- Some punches were stored unprotected in a drawer due to inadequate locations in frame. There was therefore a risk that tips could crash and it was noted that some punches appeared to have attrition damage

Quality Management Systems Deficiencies

- Incomplete or ‘late’ recording and investigation of complaints and incidents
- No regular management review of quality indicators
- Lack of Quality Improvement/CAPA processes
- Insufficient control of change
- Ineffective Self Inspection systems
- Recall systems incomplete and untested
- Non-compliance with previous inspection commitments

Quality System Documentation Deficiencies

- Lack of control of procedures and specifications
- SOP’s lacking detail or missing for certain activities
- Inadequate recording of training effectiveness
- Technical Agreements missing or incomplete
- Documentation of maintenance and calibration activities

Product Quality Reviews (PQR)

- Product Quality Reviews missing or incomplete
- There was no appropriate review and trending of the API quality attributes, excipients, and packaging components. No robust tool used to assess any trend and or variation e.g. Trends were not adequately evaluated using appropriate statistical means
- Stability data were not trended for any adverse trends
- Purified water were not included as part of PQR review for all products inspected

Supplier and Raw Material Control

- Insufficient assurance of supplier adequacy
- No evidence that API's have been manufactured to GMP
- TSE/BSE risks inadequately controlled
- No vendor recertification of secondary/backup suppliers
- No systems to address problems with suppliers
  - e.g., audit or increase testing
- Poor sampling facilities
- Insufficient identification testing

QC Laboratories

- Handling out of specification (OOS, OOE) and anomalous results aka ‘fraud’, or no OOS at all
- Lack of analytical validation
- Failure to ensure that methods are compliant with the current Pharmacopoeia
- Technical Agreements with contract laboratories- often not in place, contain insufficient detail, or are out of date and past review period
- No procedure, or procedure not being followed
- Unable to reconstruct events– poor records of investigation undertaken
- Insufficient evidence to support the conclusion made
- No assessment of GMP impact as a result of any deviations

Conclusion

- API, FPP and CRO/BE Inspections are an important part of the WHO-PQP evaluation and continuous monitoring process
- International norms, standards and guidelines are used in inspection activities to ensure wide applicability
- Inspection results shows that there are still a lot of poor manufacturing practices. Collaborative effort and skills are needed to ensure access to medicines of assured quality.

References

WHO PQP website:
http://apps.who.int/prequal/

- Prequalification of APIs
- Training material, workshops and meetings

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Questions

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Thank You

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