Quality aspects during Prequalification Evaluation of vaccines

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Outline

- Differences between vaccines and pharmaceutical
- Quality relationship
- GMP concept
- Quality aspects during PQ evaluation
- Regulatory consideration
- Programmatic considerations
- Site audit

Pharmaceuticals Vs Vaccines

Pharmaceuticals

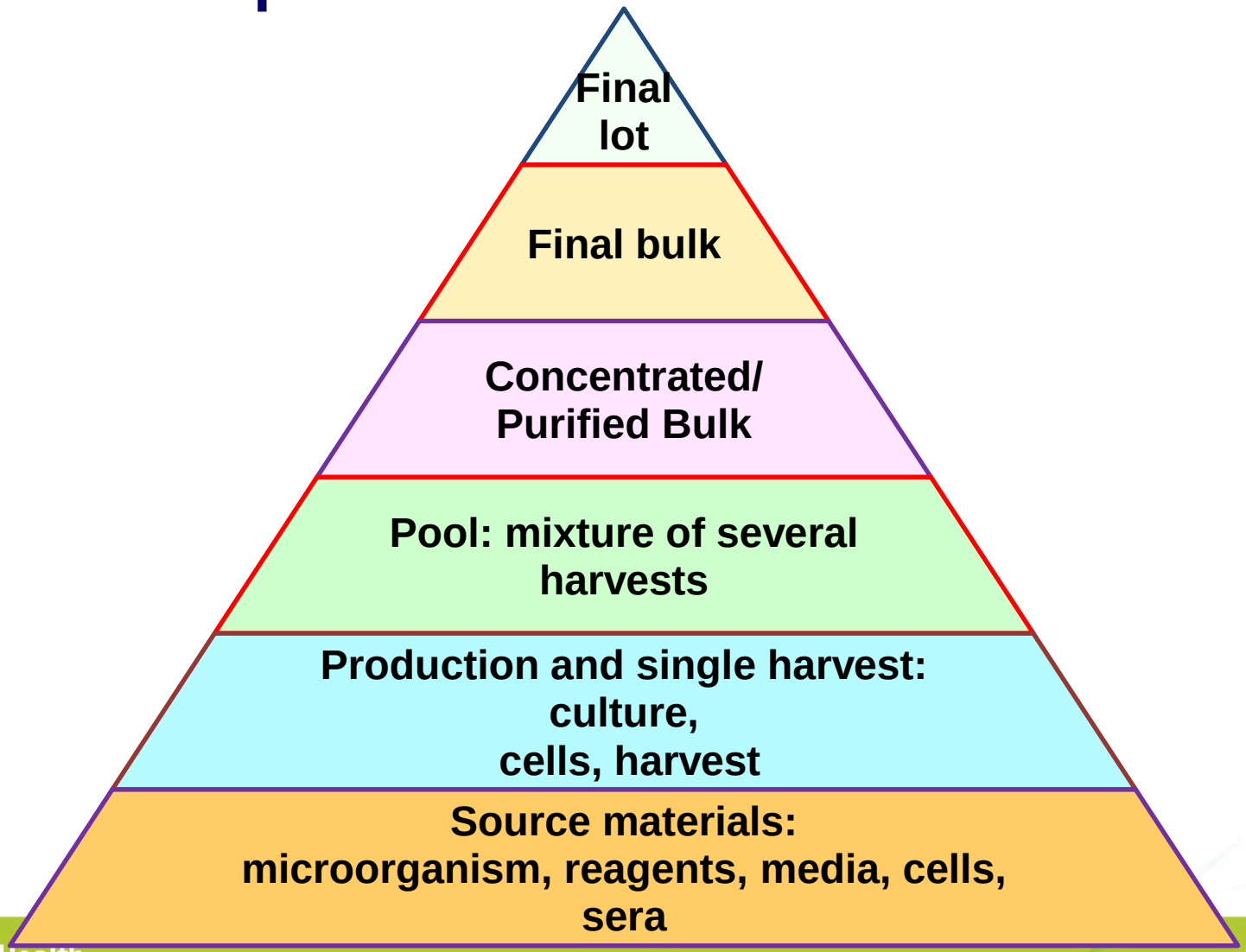
Produced and controlled using physicochemical methodologies

Vaccines

Quality considerations

- **Raw materials**
- **Manufacturing processes**
- **Quality control methodologies**

Generic vaccine production steps



Each vaccine is an unique product

- **Different strains of bacteria or viruses can be used by different manufacturers for the same vaccine**
  - **» (eg Measles: Schwartz or Edmonston Zagreb)**
- **One company may make their vaccine in many bottles, and another may make the same vaccine in a single large fermentation tank.**
- **The same virus may be grown in one type of cell by company A and in a different cell by Company B.**
- **The same vaccine from one company may not use the same stabilizers or preservatives as another company.**

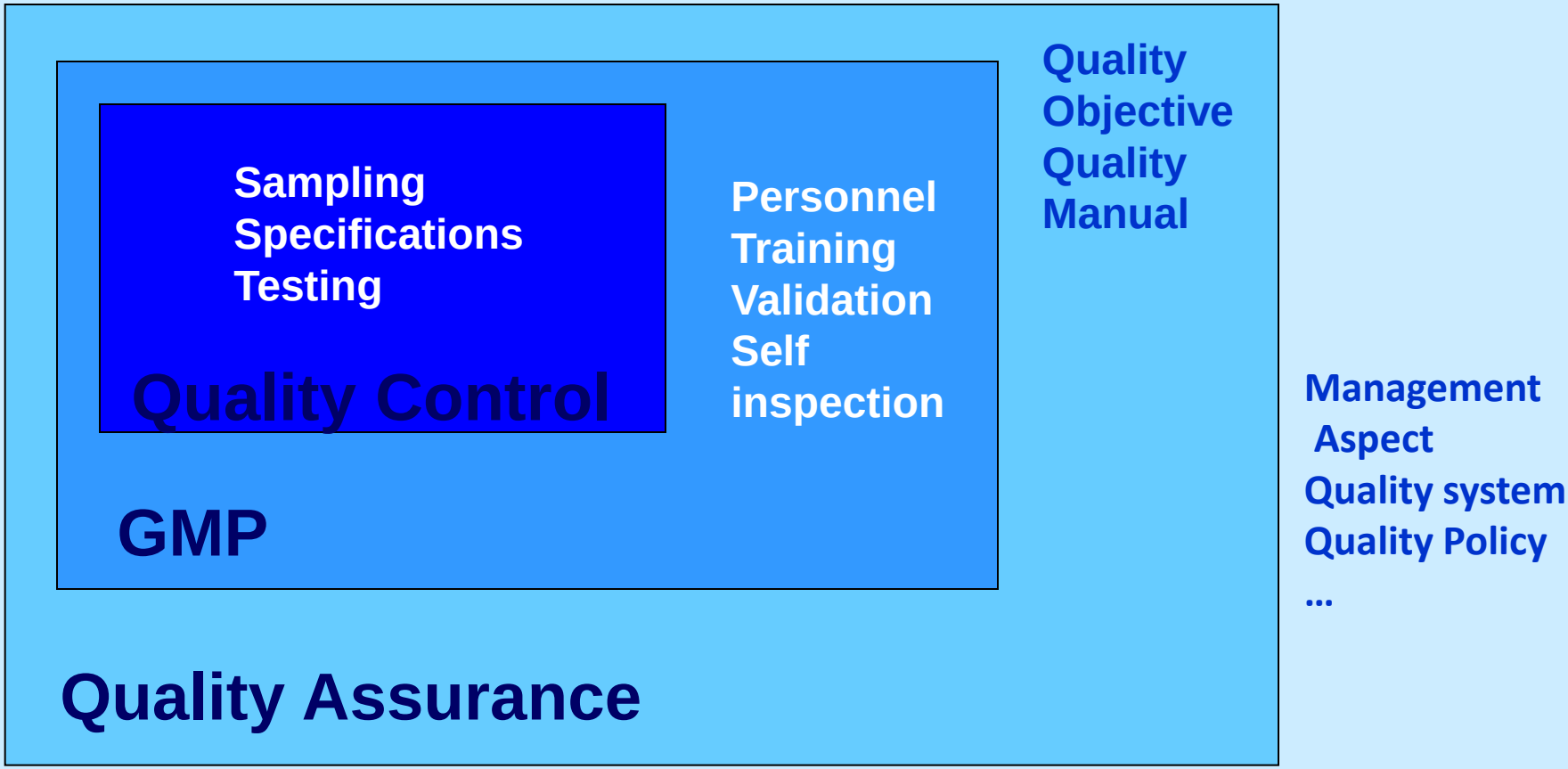
Quality Relationships

Good Manufacturing Practice (GMP)

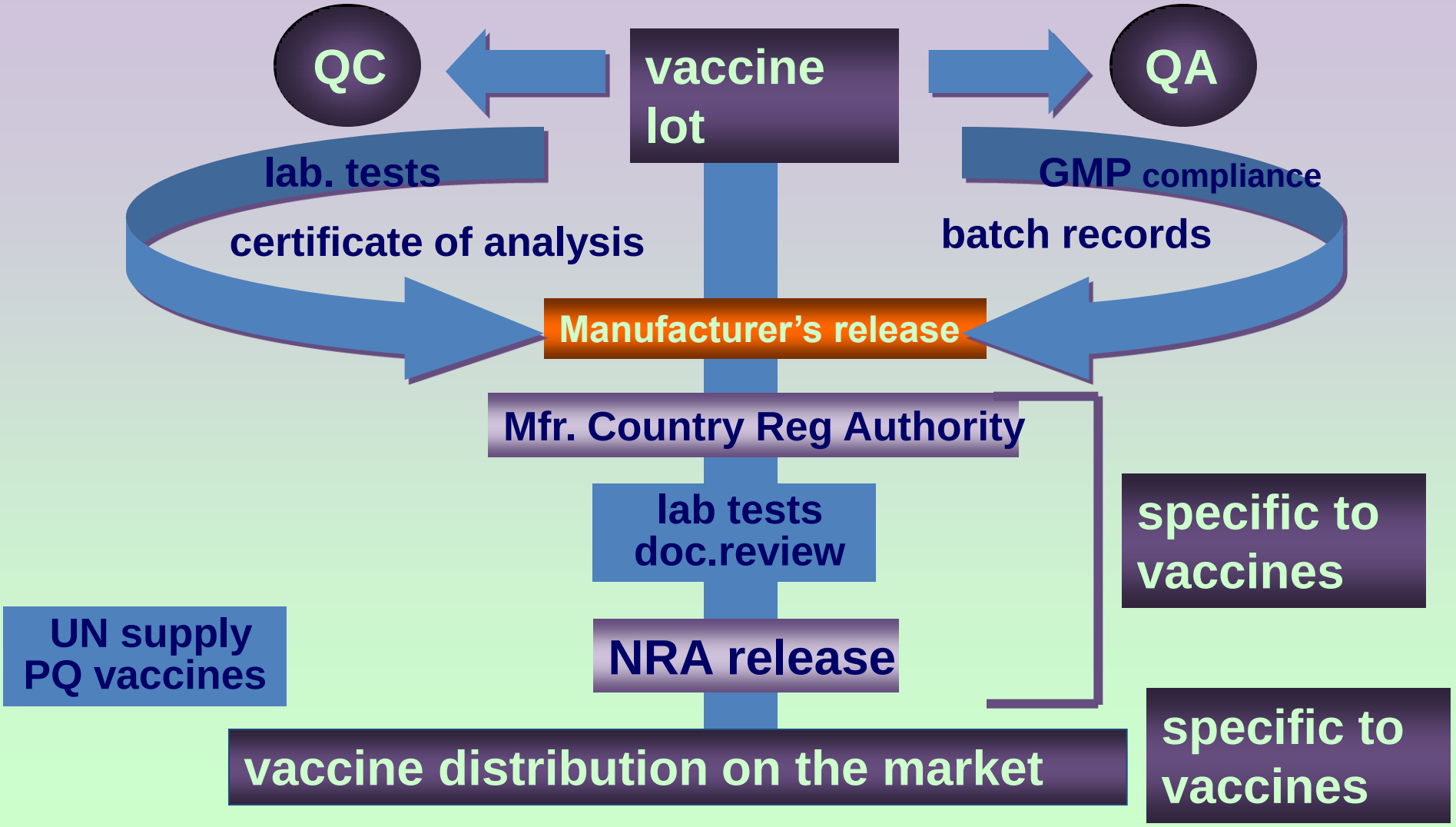
World Health Organization defines GMP as:

”that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization”

Quality Relationships



Complex release process



Quality aspects during PQ evaluation

Specific aspects considered

- General understanding of production process and quality control methods
- Production consistency at commercial scale (assessed by testing of samples of final product)
- Compliance with GMP
- Compliance with WHO recommendations and UN tender specifications including labels and inserts
- Programmatically suitable presentation
- Clinical data relevant for the target population in the recommended schedules

Chapter 5: Production

- **5.1 Manufacturing formula**
- **5.2 Description and flow chart of Manufacturing & testing**
- **5.3 General policy for process validation**
- **5.4 Handling starting material, packaging material, bulk and finished products (Sampling, quarantine, release and storage).**
- **5.5 Handling and procedures for destruction of rejected materials and products.**

Chapter 6: Quality Control (1)

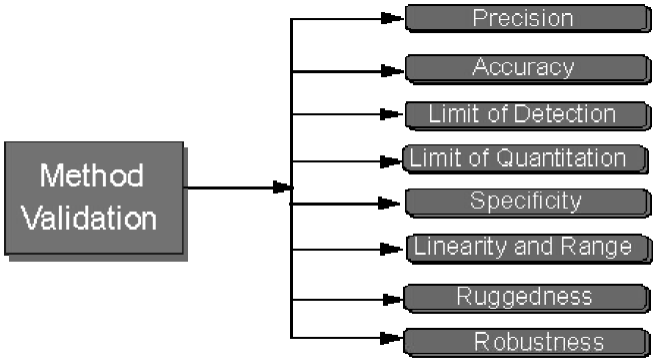
- **6.1 Starting material**
  - **6.1.1 Raw material**
  - **6.1.2 Labelling and packaging**
  - **6.1.3 Qualification of suppliers**

Chapter 6: Quality Control (2)

- 6.2 Intermediate products
- 6.3 Finished product

  Specifications and routine tests

  Validations



Chapter 7: Stability data

7.1 Intermediate products

7.2 Finished product : vaccine

7.3 Finished product : diluent & reconstituted product

7.4 Policy for assigning the date of manufacture of each component, final product and diluent

Regulatory considerations

- Need to ensure that adequate regulatory pathway is in place, that product is licensed, continuous regulatory oversight in place
- Need to assess quality
  - Adequacy of production process
  - Adequacy of quality control methods and specifications
  - Stability data
  - Transferability of testing methods to NCL and independent labs
  - Consistency of production
  - GMP compliance, adequate Quality Management System in place

Programmatic considerations (1)

- Vaccine used in the country of origin?
- Compatible with the existing EPI schedules?
- Stability profile: understanding of the cold chain requirements/ suitability for use under field conditions
- Stability profile: VVM category required
- Packaging: Volume of cold space required

Programmatic considerations (2)

- Presentation/primary packaging suitable?
- Open vial policy applicable?
- Information on inserts: adequate?, clear, reflects product characteristics? Available in all required languages?
- Transport boxes validated for international shipments?

Outcome of the review of PSF

Scenario 1: PSF review does not raise any outstanding issues

Consistency testing is scheduled

Scenario 2: PSF review raises outstanding issues for clarification/additional information (no major)

Outstanding issues may be followed up at site audit &/or request for additional information

Consistency testing is scheduled

Scenario 3: PSF review raises major technical and programmatic issues

Ad Hoc committee is convened

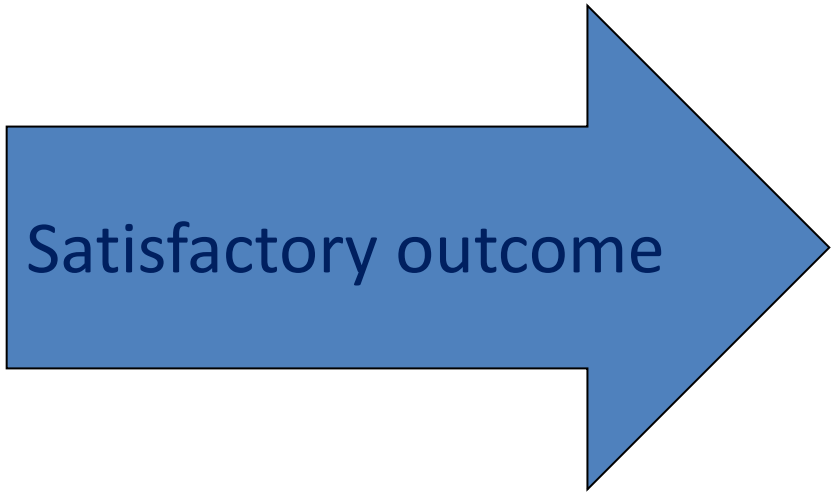
Request for additional information to give final recommendation

Stopping the PQ

Timing for site audit

File review quality and clinical completed

Consistency Testing completed



SITE AUDIT SCHEDULED

Objectives

Product is produced in accordance to WHO GMP recommended requirements

Product meets the WHO recommended requirements for quality, safety and efficacy (TRS documents)

Product meets the specifications of the UN tenders

Scope of Site Audit

- **Personnel- Organization**
- **Facilities and Equipment (Warehouses, production areas, QC laboratories, animal house, etc)**
- **Utilities**
- **Quality systems, Quality Assurance unit**
- **Production process and in process controls**
- **Quality control facilities, equipment and methods**

Aspects considered: Quality System

Quality assurance unit, roles and responsibilities

Documentation system, documentation and records control

Training program

Post-marketing surveillance, including investigation of complaints and safety and efficacy reports

Vendors qualifications

Lot release system

Investigation of complaints

Validation master plan

Aspects considered: Quality System

Handling and investigation of deviations
CAPA,
Recall, returns and destruction procedures
Reprocess, Rework and Returned Product
Internal and external audits
Personnel
Annual Product Review
Maintenance Program, pest control, environmental contro
Site master plan

Note: List is not comprehensive

Production System

Media preparation area and process

Bulk production area and process

Storage areas

In process controls

Change over procedures

Environmental monitoring

Gowning procedures

Formulation and filling

Production System

Inspection

Labeling, Packaging and Shipping procedures

Change over procedures

Change Control

Handling of Deviations

Procedures, Process and systems validation

Sanitation and hygiene: Cleaning validation

Batch manufacturing records

Note: List is not comprehensive

Quality Control System

Testing methods in place and their validation

Tests for intermediates and final products

SOPs

Sampling procedures

Stability Program

Documentation control

Quality control facilities and equipment, including animal house

Test results and trends- Handling of out of specifications

Note: List is not comprehensive

Facilities and Equipment

- Quality of construction, flow of: personnel, product, materials, wastage and process
- Utilities (HVAC, Pressure differentials, water systems, clean steam, compressed air)
- Clean rooms, Classification
- Equipment qualification: DQ, IQ, OQ and PQ
- Equipment calibration and verification
- Validation of computerized systems

Note: List is not comprehensive

Key elements for success

- **High commitment from management to Quality Products and to implementation of Quality Systems**
- **Full independence between production, Quality Control and Quality Assurance.**
- **Sound and controlled documentation system, detailed procedures (SOPs), detailed records (BPR)**
- **Well trained staff recording all data in BPR immediately, second check by supervisor. Staff trained to opening deviation reports and related investigation**
- **Presence of QA in production, major role in review of records, investigation of deviations, internal audits and CAPA system**
- **QC and QA dimensioned and equipped to match production capacity in volume and diversity of products**

Main reasons for failure

- Lack of commitment from management to Quality
- Roles and responsibilities at different levels not well defined
- Wish to rush products into the market without enough process robustness and experience
- Weak QA, weak quality systems in place not matching production needs
- Show driven by production head or directors
- Lack of transparency and honesty with auditors
- Lack of capacity to identify, investigate and correct gaps in their systems

Site Audit Outcome