Quality aspects during Prequalification Evaluation of vaccines
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

STEP I: Source materials: microorganism, reagents, media, cells, sera

STEP II: Production and single harvest: culture, cells, harvest

STEP III: Pool: mixture of several harvests

STEP IV: Concentrated/Purified Bulk

STEP V: Final bulk

STEP VI: Final lot
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

- Sampling
- Specifications
- Testing

Quality Control

- Personnel
- Training
- Responsibility
- Validation
- Self inspection

GMP
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

Quality Assurance

Quality Management

GMP

Quality Control

Sampling
Specifications
Testing

Personnel
Training
Validation
Self
inspection

Quality Objective
Quality Manual

Management
Aspect
Quality system
Quality Policy
...
WHO PREQUALIFICATION PROGRAMME

Complex release process

QC 

vaccine lot 

QA

lab. tests

GMP compliance

Mfr. Country Reg Authority

lab tests
doc. review

UN supply
PQ vaccines

NRA release

specific to vaccines

vaccine distribution on the market

specific to vaccines
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
6.2 Intermediate products
6.3 Finished product

Specifications and routine tests

Validations

- Precision
- Accuracy
- Limit of Detection
- Limit of Quantitation
- Specificity
- Linearity and Range
- Ruggedness
- Robustness
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
- Satisfactory outcome
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 control
- 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

- No issues requiring responses. Proceed to PQ

- Critical observations. Termination of PQ assessment. Company can make new application at later date

- Issues requiring responses. Develop CAPA plan for review by WHO/NRA. Desk review or second round site audit. If satisfactory, proceed to PQ