Quality aspects during Prequalification of vaccines

Jackie Fournier-Caruana
World Health Organization, EMP/RHT/PQT
fourniercaruanaj@who.int
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

Copenhagen, Denmark 23-26 November 2015
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”
Complex release process

- QC
- lab. tests
- certificate of analysis
- vaccine lot
- QA
- batch records

Manufacturer’s release

Mfr. Country Reg Authority

lab tests
doc. review

NRA release

vaccine distribution on the market

specific to vaccines

UN supply
PQ vaccines

specific to vaccines

Copenhagen, Denmark 23-26 November 2015
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 (1)

• 5.1 Manufacturing formula
• 5.2 Description and flow chart of Manufacturing & testing
• 5.3 General policy for process validation
Chapter 5: Production (2)

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

6.2.1 Specifications and routine tests

6.2.2 Validations
Chapter 6: Quality Control (3)

6.3 Finished product

6.3.1 Specifications and routine tests

6.3.2 Validations

6.3.3 List of Rejected Lots
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

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

Scenario 3: PSF review raises major technical and programmatic issues

Consistency testing is scheduled

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

Consistency testing is scheduled

Ad Hoc committee is convened
  – Request for additional information to give final recommendation
  – Stopping the PQ
Timing for site inspection

- 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
Planning the inspection: team

If more than one product will be reviewed additional experts will be proposed according to needs.
Scope of Site Inspection

• 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 inspections
- 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. **Quality Assurance has last word**
- 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 inspections 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 inspectionors
- Lack of capacity to identify, investigate and correct gaps in their systems
Site Inspection Outcome

Site Inspection Report

No issues requiring responses. Proceed to PQ

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

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