Post Prequalification monitoring activities

DCVMN meeting
Sao Paulo UNICEF, Copenhagen 8- 9 October 2014
Carmen Rodriguez Hernandez
World Health Organization, EMP/RHT/PQT
rodriguezhernandezc@who.int

Outline

- Variations
- Prequalified vaccines annual report (PQVAR)
- Reassessment
- Targeted testing program
- Monitoring of vaccine quality and cold chain complaints
- Monitoring of Adverse Events following immunization (AEFI)
- Clinical issues

Post-PQ monitoring

- Variations
- Prequalified vaccine annual reports
- Reassessment
- Targeted testing of vaccine lots
- Monitoring and responding to quality and cold chain complaints
- Responding to reports of AEFIs
- Clinical issues

Variations (1)

- **Some variations require approval by or notification to WHO before implementation for batches supplied through UN agencies.**
- **Some variations can be reported in the PQVAR only**
- **WHO will inform UN procuring agencies of variations affecting presentations or indications**
- **WHO webpage updated, as required**

Variations (2)

- Manufacturer should submit:
- Justification of the variation
- Documentation supporting the variation
- Timelines for implementation
- Approval by the National Regulatory Authority

- Additional information may be requested by WHO

Prequalified Vaccine Annual Reports (PQVAR)

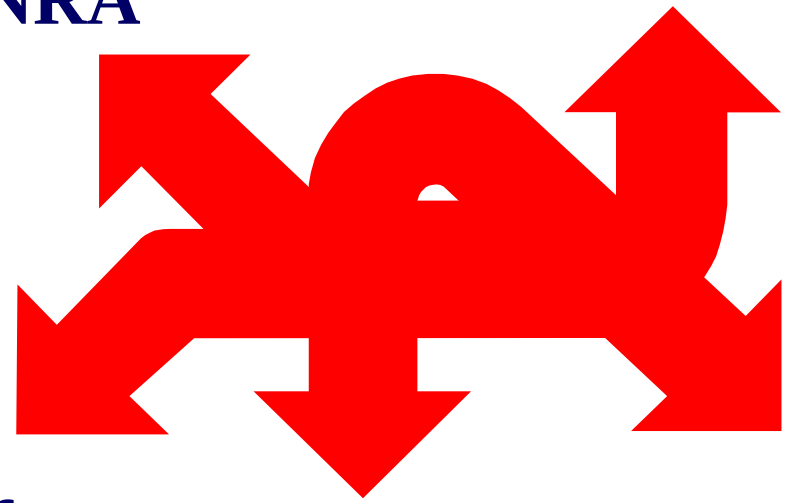
- A summary of changes/variations to the product(s) that have been implemented since the previous annual report along with copy of NRA approval
- Testing results from the ongoing stability programme
- Production and distribution data.
- GMP inspections performed since the previous annual report.
- A summary update on implementation of post-PQ commitments
- Periodic Safety Update Report

PERIODICITY of REASSESSMENT Is Risk Based

- **Information from PQVARs including:**
  - Variations implemented
  - **Rejection of batches internally or by NRA**
  - Interruptions to production
  - **PSUR**
- Quality Complaints and AEFIs received
- **Information from NRA, including inspection reports**
- Targeted testing program results
- Time since previous re/assessment
- Contribution of vaccine to UN supply

REASSESSMENT EVALUATION PRINCIPLES

Reliance on NRA



Update information on production and QC

Verification of GMP compliance (site audit)

Targeted testing results plus specific testing if required

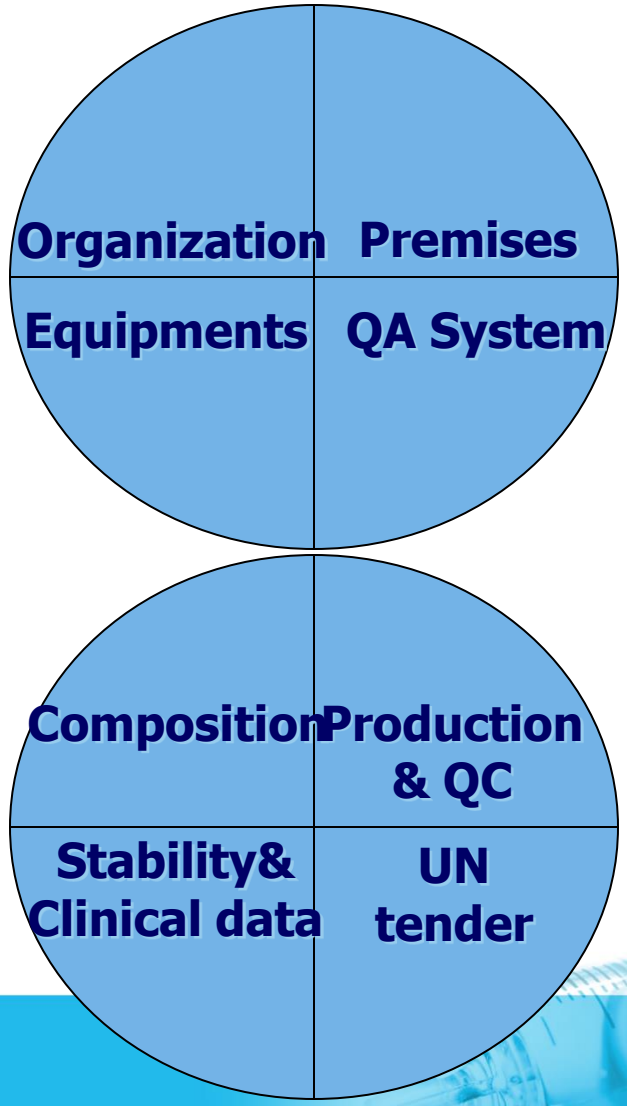
Monitoring field performance

Reassessment Process

- Review of updated PSF
- Targeted testing or specific testing of lots
- Monitoring for failure to meet specifications
- Consultation meeting with NRA
- Site audit to manufacturer jointly with NRA

Product Summary File

PSF



Manufacturer

Product

Targeted testing program

- PQ approval letter specifies samples to be retained by manufacturer from each batch supplied through UN agencies.
- Each year WHO requests manufacturers to supply a list of batches supplied to UN agencies
- WHO chooses batches for testing and requests samples, lot summary protocols and the NRA/NCL release certificates.
- Bulk, reference materials may be required
- In the event of failure to meet specifications, WHO will inform manufacturer, investigate further as required and report to procuring agencies and NRA of record for the vaccine

Vaccine quality and cold chain complaints

Main reasons

Reasons (1)

RETURN TO UNICEF COUNTRY OFFICE

unicef

VACCINE ARRIVAL REPORT (VAR)

This report is to be filled in by authorized staff, ratified by the Store Manager or the EPI Manager, and forwarded to UNICEF within 3 days of vaccine arrival. Use one report for each vaccine in the shipment.

COUNTRY	NIGERIA
REPORT No.	NPI/SW2/RI/E1/07

Date of report: 19/01/07

Place, Date and Time of Inspection	Name of Cold Store, Date and Time vaccines entered into cold store
Lagos, 18/01/07; 10.45pm	NPI, SW2 zonal cold store, 18/01/07; 10.45pm

PART I-ADVANCE NOTICE

MAIN DOCUMENTS	Date received by consignee	Copy Airway Bill (AWB)	Copy of Packing List	Copy of Invoice	Copy of Release Certificate
Pre-advice	NA				
Shipping notification	NA	Yes ☐ No ☑	Yes ☐ No ☑	Yes ☐ No ☑	Yes ☐ No ☑

List other documents (if requested)	

PART II- FLIGHT ARRIVAL DETAILS

AWB Number	Airport of Destination	Flight No	ETA as per notification		Actual time of arrival	
			Date	Time	Date	Time
57430005304	Lagos	4W2614	NA	NA	29/12/06	–

NAME OF CLEARING AGENT: JOHN HOLT SHIPPING ON BEHALF OF: UNICEF/FED. GOVT

PART III- DETAILS OF VACCINE SHIPMENT

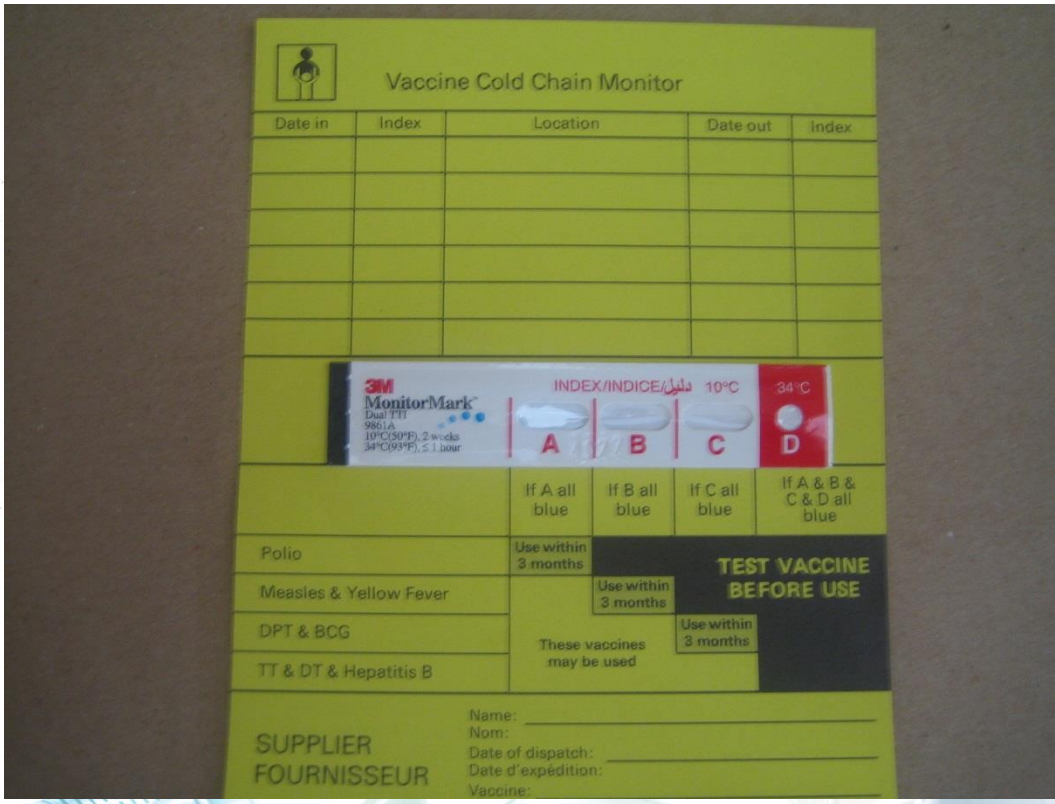
Purchase Order No.	Consignee	Vaccine Description (Type and doses/vial)	Manufacturer	Country
4507217/4501216	NPI/UNICEF	D.T.P. 10s/V	Aventis Pasteur	France

Vaccine				Diluent/droppers			
Lot Number	Number of Boxes	Number of Vials	Expiry Date	Lot Number	Number of Boxes	Number of Units	Expiry Date
Z6585-1	15	23047	31.05.08	NA			
Z6590-1	52	77822	"	"			
Z6700-1	57	82841	"	"			
A5038-1	37	54866	"	"			
A5051-1	39	57024	"	"			

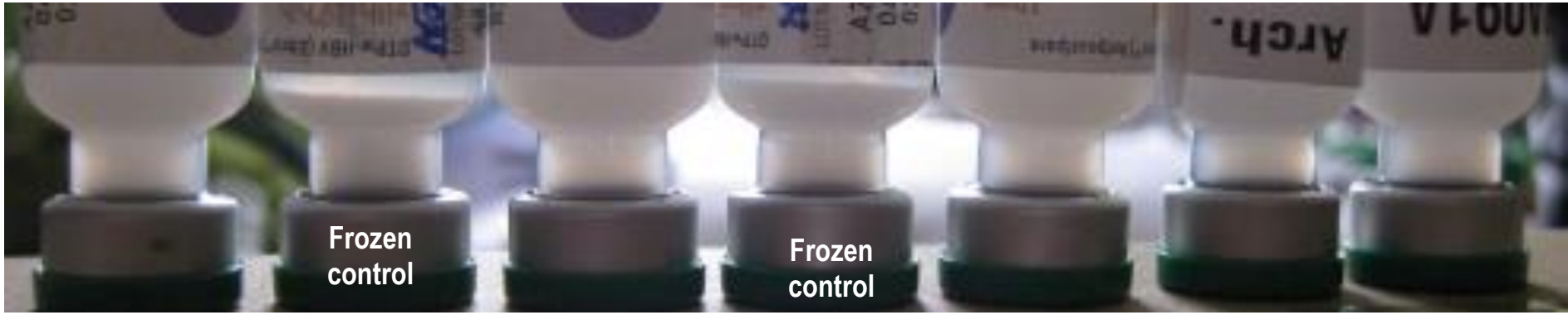
(Continue on separate sheet if necessary)

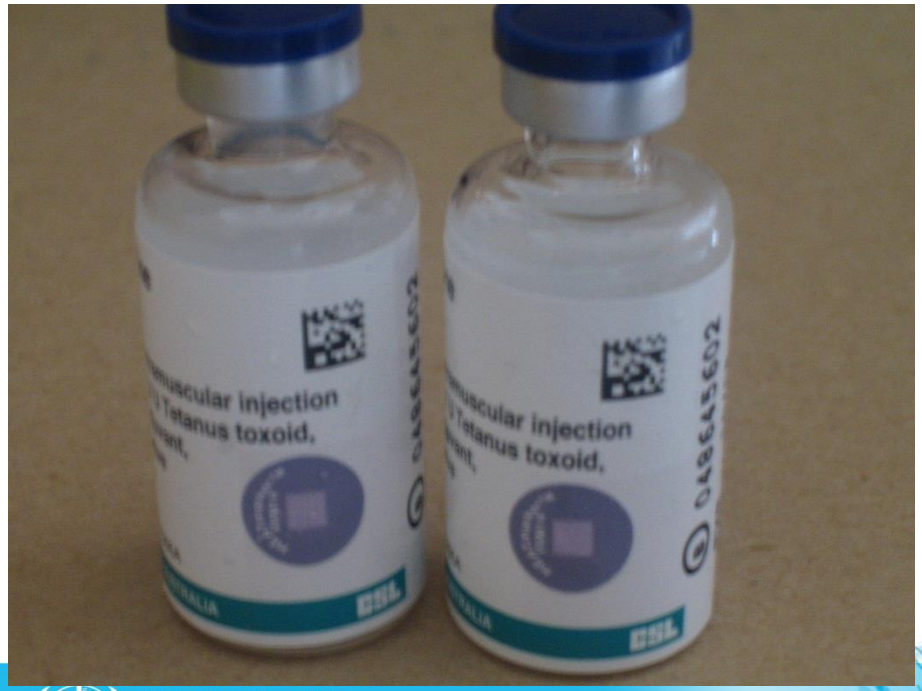
	Yes	No	Comments
Was quantity received as per shipping notification?	☐	☑	Shipping notification not received to
If not, were details of short-shipment provided prior to vaccine arrival?	☐	☑	

Shipping



Reasons (2)





Storage of the vaccine

Reasons (3)

Manufacturing

Reasons (4)

OOS testing results: Declared by the manufacturer

Change of appearance during storage

↓

Recall

Loss of potency → Recall

Accelerated stability studies

↓

Follow up

Reasons (5)

- **OOS testing results: Notified by the NCL**

- **Failure to meet appearance specifications**

Release on hold

- **Failure to meet vaccine specifications**

Eg sterility, potency

Reasons (6)

- **OOS testing results: Identified during the WHO targeted testing program**

- **Failure to meet vaccine specifications**

Eg potency

Reports of AEFI

Main reasons 2001-2011

Reasons (7)

- **Increased reactogenicity**

License and PQ withdrawal

- **Coincidental/non related**

- **Programmatic**

Vaccine handling procedures

Change of the inserts, training material and mock up samples

Other programmatic reasons  Training needs

Monitoring of complaints (1)

- **Reported by:**
  - Manufacturer
  - UN procuring Agency
  - Regional office/Countries (EPI)
  - NRAs/NCL of user countries
  - NRA/NCL of producing country
- **Examples of types of complaints**
  - Failure to meet specifications eg appearance
  - Failure to meet specifications during testing by NCLs of the user countries
  - Cold chain problems
  - VVM change of colour

Monitoring of complaints (2) Process

- WHO may request additional information to the complainant eg. lot numbers, manufacturer, packaging, pictures of the samples, information on the storage conditions and VVM status
- In case of complaints from NCLs different from the NCL exercising the regulatory oversight, review of the testing results and related documentation such as validation reports, SOPs, control charts is needed for WHO review.
- Manufacturer is requested to initiate investigation that includes review of the batch records of the lots involved in the complaint, review of the shipping procedures and monitoring devices and retesting of retention samples if applicable.
- Report of the investigation and actions performed by the manufacturer should be submitted to WHO and copied to their NRA

Monitoring of complaints (3) Process

- **NRA/NCL of the country of origin is requested to support WHO on the investigations being performed by the manufacturer and to confirm acceptability of the investigation results/report.**
- **NCL may be requested to provide testing results performed during the lot release. Retesting of retention samples may be requested if relevant.**
- **In addition the manufacturer is requested to provide:**

List of lots supplied to the complainant country

List of countries where the vaccine lots involved were distributed.

Number of doses supplied to each country.

Copy of the LSP

Complaints received from other countries and outcome of the investigations performed

Monitoring of complaints (4) Process

- WHO may perform independent testing after review of the relevant information including review of the temperature monitoring devices, review of the testing results and related data.

and routine testing

Monitoring of complaints (5) Process

- The complainant will be informed of the outcome of the investigations
- Depending on the complaint WHO may inform the relevant agencies, Regional Offices and countries procuring the same lot of the vaccine when the complaint is received, during the investigation and at the end of the investigations.
- The information may be posted in the WHO webpage

Monitoring of AEFIs (1)

Two components:

1. Safety perspective (Safety group)

Field investigation

Review of other reports of AEFIs

Causality assessment

Recommendations derived from the investigations

2. Quality perspective (PQ team)

Same process as for complaints.

Monitoring of AEFIs (2)
Testing as part of AEFIs

Testing of a vaccine lot recommended

if the clinical and/or epidemiological information about the AEFI case(s) indicates a potential vaccine quality problem and

after review of the relevant manufacturing and control documentation. The review of the batch records by the manufacturer and the NRA exercising the regulatory oversight of the vaccine allows for detection of any potential deviation during the manufacturing process that may impact on the quality of the vaccine.

The outcome of the investigation of AEFI cases would indicate

if testing is required

If so which test (s) is (are) needed.

Monitoring of AEFIs (3)
Testing as part of AEFIs

Depending on the tests to be performed, the number of un-opened containers* (sampled from the field and from the manufacturer) required for testing to be statistically calculated, so that it is powered enough to draw definitive conclusions about the relevant lot.

In the event that testing is needed, WHO will contact one of the WHO contracted laboratories that can perform the test and subsequently inform the national authorities of the number of vaccine vials to be sent as well as other logistic arrangements. Additional expertise on testing may be needed

*** Special tests opened vials**

Other issues of concern (1)

Porcine circuviruses detected in 2 rotaviruses vaccines

Management from different perspectives:

Meetings/TC with the relevant NRAs

Working group on cell substrate

GAVCS

Ad Hoc committee

Benefit/risk continued to be very favourable

Other issues of concern (2)

Suspension of the supply of pentavalent vaccine

Analysis of lots already supplied Impact?

Analysis of lots in quarantine

↓

Release of lots acceptable for supply

Analysis for restarting the manufacturing of new lots

↓

Additional CAPAs taken by the manufacturer

Strong collaboration from the NRA

Communication with relevant UN procuring agencies

Other issues of concern (3)

Addressing programmatic issues:

VVM category

Cold chain volume of current PQ vaccines

Addressing quality of PQ vaccines produced by manufacturers recalling other non PQ vaccines

Addressing quality of the outsourced bulks?

Communication issues

Increased and prompt communication to address issues of concern

Manufacturers

NRAs

Countries/Regional offices

UN agencies

Investment companies

Individuals

Webpage: Information and Qs and As document

Managing complaints/AEFIs

Training needs identified

EPI managers:

Training materials

Mock up samples

Shake tests

Monitoring devices

Quarantine and recall of vaccines

NCLs

Performance of the tests

Safety team

Vaccine safety investigations

Follow up by NRA

Post-prequalification activities

- clinical

Annual Reporting for clinical

Prequalified Vaccine Annual Report (PQVAR)

Variations

summary of changes/variations (minor)

Those requiring "approval before implementation" are assessed separately

Implementation of post-prequalification commitments

Results/update of ongoing/planned clinical trials/observational studies

Post-marketing surveillance commitments

Periodic Safety Update Report (PSUR)

Reassessments

Evaluation of the updated Product Summary File (PSF)

Ideally only sections indicated as changed will be evaluated…

PSURs and Vaccine Prequalification

PSURs can be received by WHO Vaccine PQ Secretariat in two situations:

Before prequalification

In case of new applications for PQ of vaccines already marketed for more than a year

After prequalification

PSURs should be submitted annually as part of the Prequalification Vaccine Annual Review (PQVAR) documentation

PSUR format

No specific format required

The format required by the National Regulatory Authority (NRA) of reference is accepted by WHO

Content is what matters

ICH format is accepted

PSUR evaluators

WHO staff member and /or

External expert(s) contracted by WHO

Two for the clinical evaluation of a new application of a vaccine for PQ

PSUR evaluation is just one component

Usually one in case of annual review of novel vaccines

PSUR evaluation is the sole purpose

External experts have to

sign a Confidentiality Agreement

fill in and sign a Declaration of Interests

Evaluation of the PSUR - 1

1. Background information on the vaccine product

1.1 Composition of the vaccine

1.2 Recommended schedules and routes of administration

1.3 Marketing authorization status

Evaluation of the PSUR - 2

2. Presentation of PSUR(s)

2.1 General information

2.2 Serious unlisted adverse events

2.3 Non-serious unlisted reported adverse events

2.4 Serious and non-serious listed events

2.5 Medically unconfirmed cases

2.6 Clustering

2.7 Other safety information

3. Overall safety evaluation, conclusions and recommendations

Additional considerations - 1

All dosage forms, formulations and indications for a given vaccine should be covered in one PSUR

Within a single PSUR separate presentations of data may be appropriate for different

dosage forms

indications

populations (e.g. children vs. adults)

schedules (e.g. age at administration, booster dose)

and routes of administration

Additional considerations - 2

For combination vaccines a separate PSUR is required even when its individual components, alone or in combination, are marketed individually

e.g. measles-mumps-rubella vaccine, measles-rubella vaccine, measles vaccine etc…produced by the same manufacturer