

# Post Prequalification monitoring activities

DCVMN meeting  
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# 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

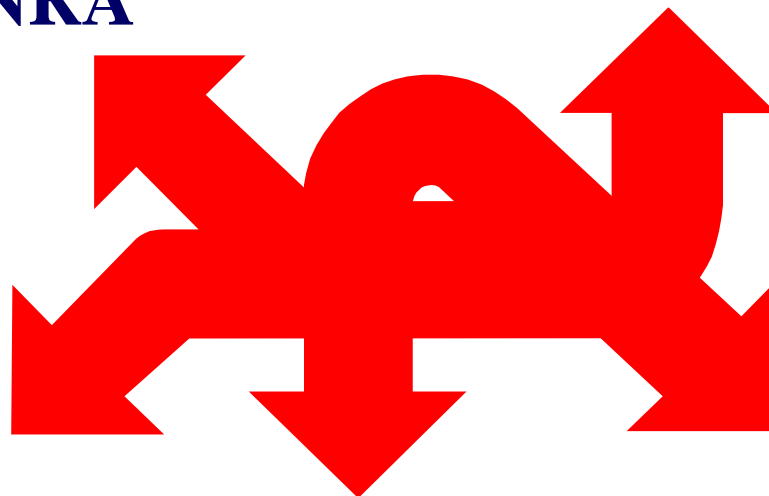
- **Information from PQVARs including:**
  - Variations implemented
  - **Rejection of batches internally or by NRA**
  - Interruptions to production
  - **PSUR**
- Quality Complaints and AEFIs received
- **Information from NRA, including inspection reports**
- Targeted testing program results
- Time 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**



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# Reassessment Process

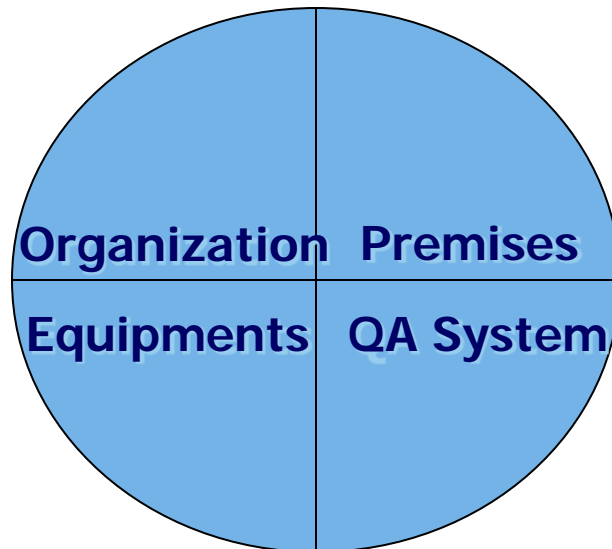
- Review of updated PSF
- Targeted testing or specific testing of lots
- Monitoring for failure to meet specifications
- Consultation meeting with NRA
- Site audit to manufacturer jointly with NRA



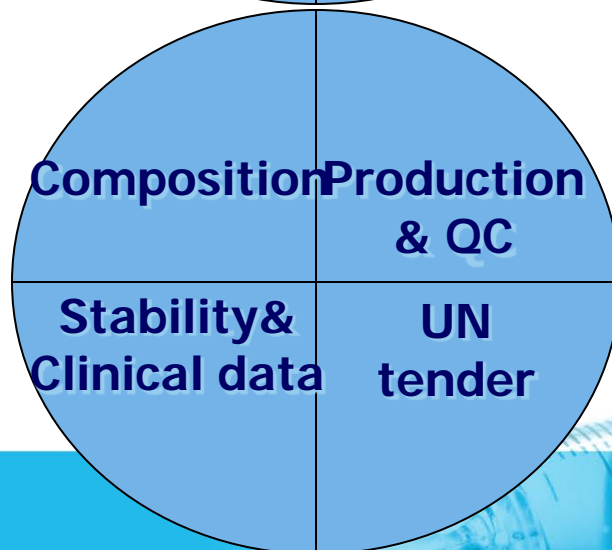


# Product Summary File

**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**



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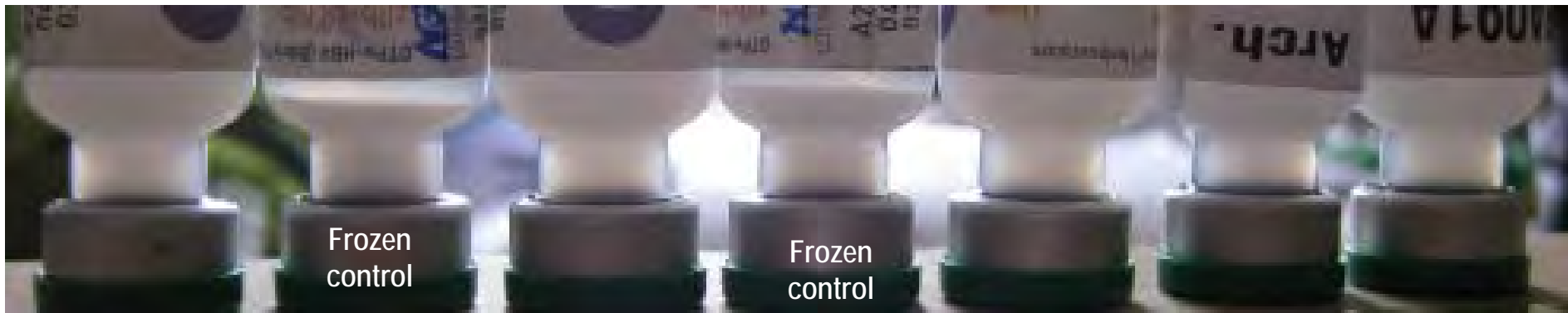
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# Shipping



## Reasons (2)



**Storage of the vaccine**



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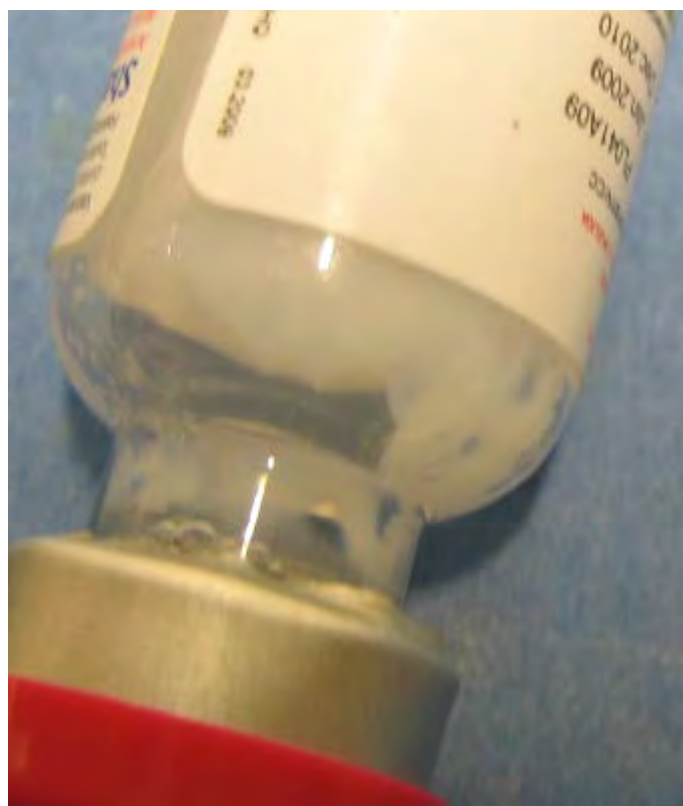
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# Reasons (3)

## 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**



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# 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



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# 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**



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# 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**



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# 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**



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# 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

