

Post-Prequalification monitoring activities

Briefing on Vaccine Prequalification for manufacturers

Buenos Aires, Argentina, October 2016

Outline of presentation

- Variations
- PSURs
- Targeted testing program
- Monitoring of vaccine quality and cold chain complaints
- Monitoring of Adverse Events following immunization (AEFI)

Variations (1)

- Approval letter for PQ indicates need for manufacturers to inform WHO regarding variations
- Three classes of variations:
 - Prior Approval
 - Annual Reporting
 - Notifications
- Guidance on variations is available
 - http://who.int/immunization_standards/vaccine_quality/variations_pq_vaccine/en/

Variations (2)

- Type N - Immediate notification - mostly administrative changes
- Type A - Variations with potential major impact on the quality, safety or efficacy of the vaccine should be approved by the NRA and reviewed by WHO before implementation
- Type R- To be submitted only in the annual report
- Supply through the UN system only after confirmation by WHO
- UN procuring agencies informed by WHO and web listing updated

Variations (3)

- Guidance document lists the type of information required in support of the variation. Information required may differ depending on compliance with conditions

N. Container closure system

Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
N1. Modification of a primary container closure system (e.g., new coating, adhesive, stopper, type of glass).	None	1 - 7	A
	1 - 3	1, 3	R

Conditions

1. No change in the type of container closure or materials of construction.
2. No change in the shape or dimensions of the container closure.

3. The change is made only to improve quality of the container and does not modify the product contact material (e.g., increase thickness of the glass vial without changing interior dimension).

Variations (4)

Supporting data

1. Product monograph, dosage forms, composition, packaging, inner and outer labels, as appropriate.
2. Process validation and / or evaluation studies, or provide equivalency rationale.
3. Information on the proposed container closure system (e.g., description, materials, specifications).
4. Results demonstrating protection against leakage, no leaching of undesirable substance, compatibility with the product, and results from the toxicity and the biological reactivity tests.
5. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
6. Long-term stability studies; results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing on three (3) finished product batches, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify the NRA and WHO PQ Secretariat any failures in the ongoing long term stability studies. Bracketing and matrixing may be acceptable if scientifically justified.
7. Information demonstrating suitability of the proposed container / closure system (e.g., last media fill's results, transportation and / or interaction studies demonstrating preservation of protein integrity and maintenance of the sterility, the sterility in multi-dose container).

Manufacturer could make reference to relevant documents (SOP, approved specifications, analytical procedures, validation and stability protocols / reports, and other studies). However, the WHO prequalification secretariat may request documented evidence.

Variations (5)

Manufacturer should submit:

- Justification of the variation
- Required Documentation supporting the variation
- Timelines for implementation
- Approval by the National Regulatory Authority

Additional information may be requested by WHO



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



Targeted testing program (1)

- Independent testing of vaccine lots supplied to UN
- Testing performed by contracted laboratories
http://www.who.int/immunization_standards/vaccine_quality/contracted_labs_vaccines/en/
- Manufacturers informed in PQ approval letter of required number of samples (vaccine dependent) to be retained from each batch of vaccine supplied through UN agencies.
- Testing program established annually
- Manufacturers provide list of batches provided through UN agencies
- Three to five lots selected by WHO and samples requested from the manufacturer.

Targeted testing program (2)

- The manufacturer to provide lot summary protocols and the NRA/NCL release certificate for each batch of vaccine submitted for testing
- In the event of out of specification results:
 - Manufacturers will be informed of test results
 - Agreement on required follow-up actions in investigation
 - As required, discuss with stakeholders (UN procurement agencies, the NRA of record, manufacturer) and provide written final report of the outcome of investigation



Quality Complaints and AEFIs

- **Quality Complaints**
 - **Temperature during transport**
 - **Breakages**
 - **Vaccine Vial Monitor colour development**
 - **Out of Specification Testing Results in Recipient countries**
 - **Labelling issues**
- **Safety Complaints /Adverse Events Following Immunisation**

Vaccine quality and cold chain complaints

RETURN TO UNICEF COUNTRY OFFICE

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.: NP/SWZ/RI/18107
 Date of report: 19/10/17

Place, Date and Time of inspection: Lagos, 18/10/17, 10:45pm
 Name of Cold Store, Date and Time vaccines entered into cold store: NP/SWZonal (Bd) 18/10/17, 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-advance	<u>NA</u>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Shipping notification	<u>NA</u>	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>

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
<u>574 300 530</u>	<u>LAGOS</u>	<u>44444</u>	<u>NA</u>	<u>24/10/17</u>

NAME OF CLEARING AGENT: JOHN HOLT SHUI ON BEHALF OF: UNICEF / FED / GOV

PART III- DETAILS OF VACCINE SHIPMENT

Purchase Order No.	Consignee	Vaccine Description (Type and dose/vol)	Manufacturer	Country
<u>45077217</u>	<u>NP/UNICEF</u>	<u>DTM-HBV (2mL)</u>	<u>ANGON</u>	<u>INDONESIA</u>

Vaccine				Diluent/droppers			
Lot Number	Number of Boxes	Number of Vials	Expiry Date	Lot Number	Number of Boxes	Number of Units	Expiry Date
<u>2 6585-1</u>	<u>15</u>	<u>23347</u>	<u>30/06/18</u>	<u>NA</u>			
<u>2 6590-1</u>	<u>52</u>	<u>77822</u>	<u>11</u>	<u>11</u>			
<u>2 6590-1</u>	<u>57</u>	<u>82541</u>	<u>11</u>	<u>11</u>			
<u>A 5038-1</u>	<u>57</u>	<u>54866</u>	<u>11</u>	<u>11</u>			
<u>A 5039-1</u>	<u>39</u>	<u>57044</u>	<u>11</u>	<u>11</u>			

(Continue on separate sheet if necessary)

Yes	No	Comments
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Was quantity received as per shipping notification?
<input type="checkbox"/>	<input checked="" type="checkbox"/>	If not, were details of short-shipment provided prior to vaccine arrival?

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Storage of the vaccine



OOS testing results:
Manufacturer
NCLs

Shipping Manufacturing

Reports of AEFI

- 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

Quality Complaints and AEFIs

PQT liaises with

- NRA of receiving country
- Procuring agencies
- WHO program staff in country
- Manufacturer
- NRA of producing country
- Safety Group in EMP department at WHO

Quality Complaints and AEFIs

PQT can :

- **Request batch record review from company**
- **Request batch distribution information from company**
- **Consider need for:**
 - **samples for testing**
 - **inspection**
 - **vaccine recall**
 - **PQ suspension or delisting**

Other issues of concern

- Porcine circoviruses detected in 2 rotaviruses vaccines
- Suspension of the supply
- Addressing programmatic issues: VVM and cold chain
- Addressing quality of PQ vaccines produced by manufacturers
- Recalling other non PQ vaccines

