WHO Prequalification of Vaccines

Post-Prequalification Activities

VAX Assessment Group
Mr. Rolando Dominguez (presenter)
Outline

• Product lifecycle & variations
• Obligations
• Other WHO Post PQ activities
  • Variations at WHO VXA
  • Complaints
  • PQVARs
Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies

(WHO TRS No. 978, 2013, Annex 6)

The manufacturer **must** inform WHO of all changes/variations that must be notified or submitted to the NRA regarding the formulation, presentation, methods of manufacture or quality control, specifications, facilities, or any other aspects that might

(a) result in a change of safety and/or efficacy of the vaccine; or
(b) change the basis of the regulatory approval of the NRA.
Life Cycle Management of WHO PQed vaccines

Are there any post-PQ requirements for PQed vaccines?

- Can changes to a PQed vaccine be made?
  – What are the requirements?
  – What changes can be made?
  – How can the changes be made?
  – What information and data should be submitted?
  – What else should be submitted?

Depending on the type of change, the applicant must notify WHO about the change in a variation application or by inclusion of the information in the annual report to the application.
Product Lifecycle Management - Variations

WHO TRS 993
Annex 4, 2014 (NRAs)
Procedures and data requirements for changes to approved vaccines.

WHO VXA
July 2015
Guidance on Variations to a PQed Vaccine.

Covers both

Adapted from Applied Clinical Trials Mar 11, 2015.
Obligations after PQ is granted

✓ Post-PQ lifecycle management activities are a key responsibility of MAHs / PQHs.
✓ It should be kept in mind that amendments to documentation, deletion and/or change to the content of a dossier will lead to a variation procedure (e.g. A, R, N).
✓ To keep dossiers updated and current.
✓ Variation procedures have been created to avoid the possibility that changes to a medicinal product may give rise to public health concerns.
# VARIATIONS - INTERNATIONAL SCENARIOS

<table>
<thead>
<tr>
<th>Variation</th>
<th>EUROPE</th>
<th>US</th>
<th>WHO VXA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type IA-IN</td>
<td>N/A</td>
<td>AR</td>
<td>N/A</td>
</tr>
<tr>
<td>Type IA</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type IB</td>
<td>30 days</td>
<td>CBE-0</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CBE-30</td>
<td>6 months</td>
</tr>
<tr>
<td>Major</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>60 days</td>
<td>PAS</td>
<td>4* moths</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A</td>
</tr>
</tbody>
</table>

Variations type **N**: Immediate Notification. VXA review within **30 days** and update the PQ documentation.

Variations type **R**: Reported **annually** as part of the PQVAR.

Variations type **A**: **Approval before implementation. Approved** by the responsible NRA. PQ approval is required before implementation in lots that are to be supplied through UN agencies.

**VXA ALWAYS RELY ON THE NRA of RECORD**
**VARIATIONS - SCOPE**

**Efficacy:** Changing in the labeling of the PQed vaccine.

**Labeling changes:** VVM, new claims based on finished studies.

**CMC changes:** New conjugation procedure; scale-up; extension of shelf life; additional manufacturing site.

*Sometime there are multiple related – continuous changes*

**IMPORTANT and good practice:**

MAHs / PQH must assess the effects of the change before distributing a drug product made with a manufacturing change (change control procedure).
B5. SCALE-UP OF THE MANUFACTURING PROCESS

<table>
<thead>
<tr>
<th>Description of the change</th>
<th>Conditions</th>
<th>Supportive</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Fermentation stage (downstream)</td>
<td>3-6, 11-13</td>
<td>3, 6, 7, 9, 11</td>
<td>A</td>
</tr>
<tr>
<td>a) Purification stage (up-stream)</td>
<td>1, 3, 5, 7</td>
<td>6, 7, 9, 11</td>
<td>A</td>
</tr>
</tbody>
</table>

**Conditions**

1. No change in the principle of the sterilization procedures of the antigen.
2. No change in the antigen specification outside of the approved limits.
3. No change in the impurity profile of the antigen outside of the approved limits.
4. The change is not due to recurring events arising during manufacture or stability concerns.
5. The change does not affect the purification process.
6. The change is not expected to impact on the quality, safety or efficacy of the final product.
7. The change in scale is linear.
8. No change in the proportionality of the raw materials (i.e., the change in scale is linear).
9. The change in scale involves the use of the same bioreactor.

**Supporting data**

3. If the change results in an increase in the number of population doublings or ........
6. Comparability of the pre and post-change antigen with respect to .............
7. Description of the batches and summary of in-process and release testing results........
9. Comparative pre-& post-change test results on characterized key stability indicating attributes......
11. Updated post-approval stability protocol and stability commitment........

A variations Type A are assessed within 90 days.
VARIATIONS

To be in compliance with WHO VX A July 2015 Guidance on Variations to a PQed Vaccine, a submission of a type A variation must include:

- A cover letter (see Appendix 4)
- A variation form (see Appendix 5)
- Documentary evidence, as per
  - Appendix 2 for manufacturing changes
  - Appendix 3 for efficacy and safety related changes

VXA ALWAYS RELY ON THE NRA of RECORD!!!!!
COMPLAINTS

➤ Vaccine quality (e.g. OOS)
➤ Vaccine safety (e.g. AEFI s)
➤ Cold chain complaints (e.g. excursions)

Initiation of the investigation: MFG + NRA

Complainant is requested to provide critical information like:
COMPLAINT/ISSUE, when and where; vaccine; batch number, expiry date; presentation; manufacturer; date; distribution data; conditions.

• Testing outcome; SOPs; trends, samples; inspection;
• VVM / recording / alarms;

VXA PQ liaise with WHO Safety & Vigilance Team (SAV).
COMPLAINTS

- Cold chain complaints (e.g. excursions)
- Vaccine quality (e.g. OOS)
- Vaccine safety (e.g. AEFI)

Depending on the outcome of the investigation

- Communication to: Mfg., NRA, UN agencies, WHO offices, WHO website
- PQ Ad Hoc Committee
Prequalified Vaccines Annual Report (PQVARs)

The manufacturer should provide a summary of variations to the product(s) that have been implemented since the previous report.

• Stability results from ongoing stability study following the stability protocol.
• Production and Distribution Data.
• GMP information.
• Post-PQ commitments.
• PSUR
Prequalified Vaccines Annual Report (PQVARs)

VXA online platform for submission and review

Module for PQVAR Submission, Screening and Evaluation

This application is introduced to streamline the procedure for annual reporting for the prequalified vaccines, with respect to submission, screening and evaluation. This electronic system is intended to facilitate and improve the process oversight.

Access for Manufacturers...

1) Create an Application Directory Service (ADS) account:
   Use the link on the left toolbar “ADS Account” to create a new ADS account.

2) Request access using your ADS account:
   Log in using your newly created ADS account. From the left toolbar, use the link “Request” to request access to this system.

3) Log in:
   Once access is granted, you will receive a confirmation e-mail, and you will be able to use that same account to log in.
PQVAR Submission: Online platform for submission and review.

WHO Guidance on Variations to a Prequalified Vaccine

- Cover Letter
- A variation Form
- Supportive data
- Evidence of a NRA approval
Post-PQ activities

<table>
<thead>
<tr>
<th>Year</th>
<th>Type A</th>
<th>Notifications</th>
<th>Annual Reports</th>
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<tbody>
<tr>
<td>2015</td>
<td>32</td>
<td>22</td>
<td>98</td>
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<td>2016</td>
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<td>2017</td>
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<td>22</td>
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<td>2018</td>
<td>44</td>
<td>18</td>
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</tr>
<tr>
<td>2019</td>
<td>46</td>
<td>28</td>
<td>117</td>
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THANK YOU!!!!!!