Assuring vaccine quality: Overview of Prequalification

Vaccine Industry Consultation
UNICEF, Copenhagen 8-9 October 2014
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Outline

• Overview on Prequalification
• Programmatic suitability for PQ
• Strategic priorities
• Activities to facilitate access of vaccines:
  • Vaccine vial monitor
  • Control temperature chain
  • Shipping guidelines
  • Accelerated registration of prequalified medicinal products
• Polio eradication and end game strategy
• Activities to facilitate license of IPV and bOPV
• Path forward
Prequalification

• Ensures the quality, efficacy and safety of medicines, vaccines and immunization devices and diagnostics.

• Medicines:
  – Prequalification programme for medicines (finished dosage forms)
  – Prequalification of active pharmaceutical ingredients (APIs)
  – Prequalification of quality control (QC) laboratories
  – expanding access to priority essential medicines: HIV/AIDS, tuberculosis, Malaria, Reproductive Health and some other disease categories (e.g. NTD)

• Vaccines and immunization devices:
  – Ensures that candidate vaccines are suitable for the target population and meet the needs of the programme
Prequalification is NOT stand alone activity
Many other technical work areas support and link to prequalification (medicines, vaccines, diagnostics and medical devices)

• Outside EMP – Disease oriented departments/programs, IVB Department, Strategic Advisory Group of Experts (SAGE) on Immunization; Regional and Country Offices
• Inside EMP – Norms and standards work/Quality Assurance, Safety/Vigilance, Activities to combat SFFC medical products, NRA strengthening, Policy, Innovation and technology transfer

New prequalification team: five functional groups

- **PQT Coordinator**
  - **Inspections services**
    - Deus Mubangizi
  - **Technical assistance and laboratory services**
    - Milan Smid
  - **Medicines assessment**
    - Matthias Stahl
  - **Vaccines assessment**
    - Carmen Rodriguez
  - **Diagnostics assessment**
    - Irena Prat
WHO uses the same scientific principles to assess the products safety, quality and efficacy/performance as well-resourced national regulators:

- Scientific assessment of documentary evidence for quality, safety and efficacy
- Assessment of suitability for use of the vaccine in the intended settings
- Site inspections for GMP, GLP and GCP
- Control of variations to products and their manufacturing processes
- Post-approval monitoring of quality and safety
Extensive multilayer collaboration: working with regulators … for regulators

- Not duplicating work done by stringent regulatory authorities
  - SRA approval of new and generic products – abridged procedure
  - US FDA tentative approvals – based on confidentiality agreement including in the PQ products list
  - European Medicines Agency (EMA) – Art 58 … and beyond
  - Collaboration with EDQM, in particular in the area of APIs (confidentiality agreements with US FDA, EDQM, EMA …)

- Active participation and involvement of
  - Regulatory authority experts from well resourced and less resourced settings WORKING TOGETHER for common goal
Purpose of WHO vaccines prequalification programme

A service provided to UN purchasing agencies.
Provides independent opinion/advice on the quality, safety and efficacy of vaccines for purchase
Ensures that candidate vaccines are suitable for the target population and meet the needs of the programme
Ensures continuing compliance with specifications and established standards of quality
Principles

Reliance on NRA

Meeting WHO requirements and tender specifications

Consistency of final product characteristics

Clinical data

GMP
Pre-conditions for PQ evaluation

Reliance on the National Regulatory Authority (NRA) of the exporting country

NRA must be assessed as functional as a result of successful evaluation using the WHO NRA assessment tool.

NRA’s functional status needs to be sustained over time.

Continued regulatory oversight by NRA is required as well as communication with WHO about potential problems with the vaccine.

Agreements are established with the NRAs for information exchange when a vaccine is about to be prequalified.
Pre-conditions for PQ evaluation

- Vaccine is licensed/registered by the responsible NRA (Scientific opinion by EMA accepted)
- WHO guidelines/recommendations approved by the ECBS are available (published in the WHO Technical Report Series)
- Listed in the vaccine priority list (low priority vaccines may be postponed depending on workload and no priority vaccines will not be reviewed)
Prequalification process

- Scientific review of quality dossier
- Scientific review of clinical data
- Testing of samples
- Consultation with responsible NRA
- Site audit to manufacturing facilities

Revised procedure in place from January 2012
Role of NRA during PQ process

As part of the evaluation procedure, consultation with NRA

To discuss regulatory status of the concerned vaccine/s
Clinical performance in country of manufacture if used
Quality evaluation, outcome of recent GMP inspections
Compliance with specifications (trends from lot release data)
Regulatory actions
Informal agreement for information sharing with WHO recorded in Consultation report
Monitoring performance of PQd vaccines

Targeted testing by WHO contracted labs: Once a year testing of samples of lots shipped to countries to ensure continuing compliance with specifications

Monitoring and resolution of complaints and reports of AEFI (with collaboration of the responsible NRA)

Reassessments frequency defined on risk analysis basis
Why is Vaccines PQ important for user countries and its NRAs?

It represents a source of vaccines of "assured quality"
In addition the evaluation is focused on programmatic needs
WHO follows up on complaints and reports of AEFIs and publishes the outcome of investigations
WHO monitors the quality of prequalified vaccines on a continuing basis, through testing of samples, reassessment of the products, targeted audits, and delists vaccines if they do not meet the established specifications and/or standard
Opportunity for NRAs in user countries to save resources to focus on other priorities, since registration can be granted through a facilitated and shortened procedure
Programmatic suitability and its assessment

- Vaccines produced in developed countries may not have taken into account programmatic challenges in developing countries.
- Examples:
  - Non auto-disable prefilled syringe presentations
  - Stability of components in the event of cold chain breakdown

- WHO PQT has always considered programmatic suitability but it was in 2012 that a written guidance (PSPQ) was developed and put in place
Objectives of PSPQ

- Judge the programmatic suitability against defined mandatory, critical and preferred characteristics

Benefits of PSPQ

- Give clear directions to vaccine industry before submission
- Reduce decision making time
Submission screening and SC assessment

- Upon receipt, product summary files (PSFs) are screened for completeness and compliance with the required format and contents by the PQ secretariat.
- PSFs are also screened by the PQ Secretariat for compliance with programmatic suitability criteria,
  - if mandatory characteristics are not met the PSF is rejected.
  - if the PQ Secretariat identifies a deviation from the critical characteristics or finds a unique characteristic, the product will be referred to the PSPQ Standing Committee for independent review of the characteristic.
- For vaccines where vaccine supply and availability is taken into account in formulating the PSPQ SC recommendation, the formal input from UNICEF SD and the PAHO Revolving Fund should be sought on the supply and availability of similar vaccines through the PQ Secretariat.
PSPQ Current status

• Revised document endorsed by Immunization Practices Advisory Committee (IPAC) 11-12 June 2014 IPAC
The new PSPQ requirements will come into effect on 1 January 2015.

**Main changes:**
(1) Antimicrobial preservatives and the definition of “inadequately preserved” vaccines;
(2) antigenic stability for 28 days;
(3) the management of vaccines that were pre-qualified prior to the PSPQ implementation (grandfathering);
(4) new mandatory and preferred characteristics and the transition to critical characteristics.
Main changes related to MDVP

Liquid multidose vials:

The vaccine presented for prequalification should be adequately preserved (WHO/EPI).

This is defined by having either the thiomersal concentration of >25 μg per dose (0.5ml) for monovalent hepatitis B vaccine and >50 μg per dose (0.5ml) for other vaccines) or the preservative having demonstrated its anti-microbial efficacy to control contamination for 28 days using the EU pharmacopoeia preservative efficacy test according to the “B” criteria of acceptance.
Main changes related to MDVP

Lyophilized multidose vials (antigenic stability)

For the application of the Multi-Dose Vial Policy (MDVP), a decision will be made if a multi-dose vial can be safely kept open for subsequent vaccination sessions, or if the vial should be discarded at the end of the session. For this decision to be made, vaccine manufacturers are required to include in the PSF dossier submitted for PQ data on the antigenic stability of the vaccine for 28 days after reconstitution. These data will not be used to determine if the vaccine should or should not be pre-qualified, but (together with data on preservative efficacy) will enable the appropriate classification of the vaccine in respect of the MDVP. This decision will be made by the PQ Secretariat, based on the review of the data available to the PQ team. Should the vaccine have been referred to the PSPQ Standing Committee, the Standing Committee may make a recommendation on this decision, and the antigenic stability will then be taken into consideration.

Thus, for PQ, the decision on whether an opened vaccine vial should be discarded at the end of the session is an outcome of this process, not a criteria in deciding whether to start the prequalification assessment of a vaccine.
New preferred characteristic

Preferred characteristics will not be reviewed or assessed by the PSPQ SC because these characteristics will not directly influence the prequalification process. However, it is expected that national immunization programmes and procuring agencies will select vaccines with these preferred characteristics over those vaccines that do not meet these characteristics. Compliance with preferred characteristics is not compulsory, although with time these characteristics may become ‘critical’ characteristics.

Two preferred characteristics are scheduled to move to become ‘critical’ characteristics during the next PSPQ revision in two to three years. These criteria (labelling and barcoding)
## Preferred characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Maximum packed volume</td>
<td>A smaller packed volume is preferred. Where appropriate, components should be packed/shipped together</td>
</tr>
<tr>
<td>Dose volume</td>
<td>Smaller volumes and standardized volumes are preferred</td>
</tr>
<tr>
<td>Doses per primary container, non-campaign setting</td>
<td>Vials with ≤10 doses per vial are preferred. Minimize number of doses per vial that cannot be reused in subsequent sessions once the container is open.</td>
</tr>
<tr>
<td>Doses per primary container, campaign setting</td>
<td>Vials with ≥ 10 doses per vial are preferred</td>
</tr>
<tr>
<td>Process of preparation for administration</td>
<td>Single component/ready to use (e.g., liquid). For multi-component vaccines, provide vaccines in formats to minimise (1) number of reconstitution steps, and (2) potential for error during preparation and administration.</td>
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</table>
## Preferred characteristics

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<tr>
<td>Thermo stability / storage</td>
<td>• Vaccines and diluents that can be stored for extended periods at temperatures above +8°C are preferred.</td>
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<tr>
<td></td>
<td>• Vaccines with data and licencing allowing for higher temperature storage. If feasible, use 40°C as the current target threshold temperature.</td>
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<tr>
<td>Freeze sensitivity</td>
<td>Vaccines that are not damaged by freezing temperatures (＜0°C) are preferred</td>
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<tr>
<td>Materials, primary and sec. packaging and injection material</td>
<td>Materials for delivery devices, primary containers and secondary and tertiary packaging that minimize environmental impact of waste disposal are preferred</td>
</tr>
<tr>
<td>Secondary packaging, diluents and vaccines</td>
<td>• Diluents and vaccines should have the corresponding number of doses per secondary container.</td>
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</table>
## Preferred characteristics

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| Delivery devices       | • The use of novel delivery devices that reduce risk of contamination are encouraged.  
                          • The use of a compact prefilled auto-disable injection system (eg. UniJect®) is encouraged.                                      |
| Labelling              | • Primary and secondary containers should be labelled according to the principles set out in the proposed amendments to TRS 822.      |
| **Planned for transition to critical criteria in next revision** |                                                                                                                                         |
| Barcodes               | • Bar codes are recommended on secondary and tertiary packaging and should conform to GS1 standards and associated specifications.         |
| **Planned for transition to critical criteria in next revision** |                                                                                                                                         |
Strategic priorities

- Secure the supply base for priority medicines
- Facilitate access to quality products for developing countries
- Improve efficiency of the prequalification procedure
- Expand portfolio according to needs and options for introduction
Supply Security

Monitor closely the performance of prequalified vaccines including FU audits and conducting production capacity assessments.

Actively seek for additional sources for priority vaccines.

Secure the supply base for priority vaccines for developing countries.

Establish risk mitigation strategies in case of failure of NRA.
## Access

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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<tbody>
<tr>
<td>Single standard of quality (WHO recommended requirements)</td>
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<tr>
<td>Consolidated investigation, reporting and communication in response to quality or safety concerns</td>
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<tr>
<td>Implementation of an expedited/facilitated registration procedure for prequalified vaccines in receiving countries</td>
<td></td>
</tr>
<tr>
<td>Mechanisms to minimize wastage of vaccines, facilitate outreach (VVMs, MDVP, CTC)</td>
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</tbody>
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Facilitate access to quality products for developing countries
Vaccine vial monitor

Programmatic Challenges:

- VVM category
- Similar type of vaccine

Stability data matching VVM category

Custom made VVM
Contribution development of Controlled Temperature Chain Project Optimize: PATH/WHO

Transport to health centre
Allow specific vaccines to be kept and administered at ambient temperatures, up to 40°C
For one, limited period of time immediately preceding administration
For vaccines meeting a number of stability conditions

Current focus: vaccines administered during campaigns and special strategies:
eg Meningo conjugate A, Yellow Fever, Pneumo, Hepatitis B, Rota, Cholera

Manufacturers
Studies to enable on label use of vaccines under CTC and regulatory submissions

Regulators
Regulatory pathways
Review data for licensing under CTC

WHO
CTC Guidelines (Norms)
Work w/ regulators to define Regulatory Pathways and prequalification (vPQ)
Field studies to show programmatic challenges, opportunities, and impact of CTC (EPI-IVB)
Shipping guidelines

UNICEF study on the use of shipping containers and tertiary/secondary packaging by countries. Outcome will be considered for the revision of the Guidelines for international shipments.

Packaging harmonization VPPAG to be finalized

Meeting in 2015 with UNICEF SD to review all concerns regarding international shipment vis-à-vis the guidelines.

Discussions will take place on the use of gel packs to prevent freezing (criteria: biodegradable, non-toxic, clear instructions of use and disposal)

Need to work on a common SOP in resolving issues/complaints when T° excursions/alarms
Accelerated registration of WHO prequalified vaccines

**Objective**
Assist countries to adopt a facilitated, expedited procedure for the national registration of prequalified vaccines.

**Who can benefit**
- Countries procuring through UN agencies
- and/or
- Countries procuring directly but requiring WHO prequalification as a tender condition
  where the national regulations include provisions to shorten the normal regulatory approval process.
Implementation of Procedure for expedited review of imported prequalified vaccines for use in national immunization programmes (WHO/IVB/07.08)

Firstly used for registration of MenAfriVac in 26 countries of the belt
Accelerated national registration of WHO-prequalified pharmaceutical products and vaccines.

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Pharmaceuticals</th>
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<tbody>
<tr>
<td>Procedure for expedited review of imported prequalified vaccines for use in national immunization programmes (WHO/IVB/07.08)</td>
<td>Collaborative procedure between the World Health Organization Prequalification of Medicines Programme and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products.</td>
</tr>
<tr>
<td>Expert Committee on Biological standardization</td>
<td>Expert Committee on Specifications for Pharmaceutical Preparations</td>
</tr>
<tr>
<td>Firstly used for registration of MenAfriVac in 26 countries of the meningitis belt</td>
<td>Procedure in place since 2012 Collaborative agreements signed with 20 National Regulatory authorities 33 procedures finalized Details on <a href="http://www.who.int/prequal">www.who.int/prequal</a></td>
</tr>
</tbody>
</table>
Revision of procedure

- WHO
- NRA
- Manufacturers

Agreement

Facilitated license
Principles of collaborative registration (1)

1. Interested National Regulatory Authorities (NRAs) agree to respect principles of the Collaboration as regards sharing of complete confidential assessment and inspection outcomes and acceleration of regulatory approvals.

2. The company submits to the NRA the dossier with same technical data in CTD/PSF format, and provides agreement to share information among NRA and PQT. Fees to NRA follow national requirements.

3. WHO/PQT shares the confidential assessment reports, inspection reports, and laboratory results via a secured website to designated NRA focal persons. Advice and consultations provided if necessary.
Principles of collaborative registration (2)

4. The NRA uses shared information at its discretion – e.g. for acceptance, verification, quality assurance, training. NRA is committed to decide within 90 days. NRA informs WHO/PQT about its decision and justifies, if deviating in its decision from WHO/PQT.

5. The procedure includes provisions for variations and for notification of suspensions and withdrawals of prequalified product both ways (NRAs and WHO/PQT).
Joint collaborative procedure for pharmaceuticals and vaccines: Path forward

- Discussion with stakeholders started
- Pilot for vaccines is under preparation
- Endorsement by relevant expert committees expected in 2015
- Extension of current agreements with NMRAs to vaccines (potentially also Diagnostics)
- Based on collaboration agreements, full reliance on PQ as potential mechanism for accelerated registration of products for emergency use.
- Newcomers are welcome to participate!
The Strategic Advisory Group of Experts on Immunization (SAGE), recommended in 2012 the withdrawal of the type 2 component of oral polio vaccine (OPV) from routine immunization programmes in all countries, facilitated by the introduction of at least one dose of IPV.

Weekly epidemiological record wer 8901

The last case of wild poliovirus type 2 (WPV2) was seen in 1999.

88% of the total of the circulating vaccine derived poliovirus (cVDPV) cases in recent years were caused by the vaccine derived type 2 strain.

Introduction of IPV by 2015 and bOPV by 2016 in all countries.

www.who.int/immunization/diseases/poliomyelitis/inactivated_polio_vaccine/en/
www.polioeradication.org
Facilitating license of IPV: PQ pathway

WHO

NRA

Manufacturers

Agreement

Joint review

Facilitated license
Path forward facilitating license of IPV

Joint review

**AFRO countries**
20-24 October 2014 Turkey

- Francophone countries: Benin, Burkina Faso, Cameroon, Côte d’Ivoire, Mali, Senegal, Togo
- Anglophone countries: Botswana, Ethiopia, Ghana, Sierra Leone, Tanzania, Uganda, Zambia, Zimbabwe : ENGLISH

**SEARO countries**
10-14 November Thailand

- Bhutan, Myanmar and Sri Lanka
Path forward: IPV and bOPV

• Ensuring license of IPV vaccine
• Ensuring licensing of variations (IPV).
• WHA resolution to facilitate bOPV introduction
• Facilitating license of bOPV:
  • Discussion of Collaborative agreement concept.
  • AFRO and SEARO countries: October-November 2014
  • Extension of collaborative agreements to vaccines
  • New agreements (pharmaceuticals and vaccines)
  • Advocacy workshop: EURO and PAHO (December 2014, Q1 2015)
  • Other regions: 2015
Additional information

Variations document to prequalified vaccines:
Published in the webpage in 2013
Comments received
Final version to be published in the webpage
Summary

• Prequalification system ensures the quality, efficacy and safety of medicines, vaccines and immunization devices and diagnostics for global use.
• Facilitate access to quality products for developing countries
• The collaborative registration of PQed medicines is a work-sharing and confidential information sharing mechanism, which already produces results: in 80% of 33 procedures registration was granted in less than 90 days.
• Multiple benefits are seen for participating NMRAs, manufacturers and WHO (e.g., facilitated decision making, learning, harmonization of dossiers, assurance about the same product, faster access, life cycle management).
• Based on collaboration agreements, full reliance on PQ as potential mechanism for accelerated registration of products for emergency use.
Relevant PQ information

http://www.who.int/immunization_standards/vaccine_quality/pq_system/en/
http://www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/
http://www.who.int/immunization_standards/vaccine_quality/ps_pq/en/
http://www.who.int/immunization_standards/vaccine_quality/expedited_review/en/