#### Update on Vaccines Prequalification

#### International Workshop on "Vaccine Quality Management Systems: Approaches to Risk assessment."

October 24 - 25th 2013 Rio de Janeiro, Brazil Dr. Nora Dellepiane, Coordinator Regulatory Systems Strengthening

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## **Outline of presentation**

- What is the purpose of the programme
- What are the principles
- Steps of the procedure
- How does it compare to a MA
- Who benefits
- Preconditions for evaluation



- Features of the revised procedure (streamlining and PSPQ)
- Why is PQ important for manufacturers
- Main issues faced during the process
- Support provided



## What is the purpose of the WHO Prequalification Programme?

It is a service provided by the WHO Medicines Department to United Nations Procurement Agencies to advise them on the <u>quality, safety</u> and efficacy of medicinal products

In the case of the vaccines programme, the focus is also on <u>suitability</u> <u>of the product</u> for use in National Immunization Programmes globally

Vaccine meets the needs of the programme reflected in the UN tender specifications



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## What are the principles followed



## **Steps of the PQ procedure**

- 1. Screening of dossier (Product Summary file or CTD) for quality, clinical and product characteristics
- 2. Payment of fees: Day 0
- **3.** Scientific review of dossier (quality, clinical, GMP)
- 4. Testing of samples for consistency of final product characteristics
- 5. Consultation with responsible NRA
- 6. Site audit of manufacturing facilities with representatives from NRA as observers





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### How does it compare to a marketing authorization

Aspects considered		Exporting Country NRA	WHO prequalification procedure
Chemico pharmaceutical and biological		Exhaustive review	Review of summary information
Non-clinical data		Exhaustive review	
Clinical data		Relevance of data to exporting country	Relevance of data to UN target population
GMP		Compliance with National standard	Compliance with WHO standard
Consistency testing		Sometimes	Always
Programmatic characteristics	Schedule, co- administration	Relevance to exporting country	Relevance to UN population
	Stability profile & shelf life	Suitability for exporting country	Suitability for developing countries + VVM
	Applicability of multidose vial policy		Assessed
	Presentation	Highly flexible in most cases	Critical: vials and AD syringes
UN tender specifications			Reviewed: need to be met
Labelling and packaging			Specific to UN
Shipping boxes (tertiary packaging)			Validation assessed



## Who benefits



#### **Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. TRS 978, 2010 Annex 6**



#### http://www.who.int/immunization\_standards/vaccine\_quality/pq \_\_suppliers/en/index.htm



## Notes for guidance for manufacturers

- Guideline for the preparation of the Product Summary File for vaccine prequalification
- Clinical considerations for evaluation of vaccines for prequalification
- Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification WHO/IVB/12.10
- Guide to Master Formula
- Environmental Monitoring of clean rooms in vaccine manufacturing facilities
- Priority setting for WHO vaccines prequalification programme
- Guidance on variations to prequalified vaccines (under preparation)
- Validation of production process for vaccines and other Biologicals-Compliance expectations (under preparation)
- Deviations handling and Quality Risk Management (under preparation)



#### **Fundamental pre-condition 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 by a team of experts 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

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## **Other pre-conditions for PQ evaluation**

- Candidate vaccine is on WHO priority list for evaluation
- WHO recommendations for the vaccine of interest are available (published in the Technical Report Series)
- Vaccine is registered by the responsible NRA (or received a positive scientific opinion under article 58 by EMA)
- The vaccine meets mandatory characteristics for programmatic suitability



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## Features of the revised procedure Streamlined prequalification evaluation

- Introduced option for increased collaboration with mature National Regulatory Authorities (NRAs) to <u>streamline the PQ</u> <u>procedure</u>
  - Confidentiality and Collaboration agreements being signed with eligible NRAs: US, Canada, EMA, Australia, France, Belgium and Italy
  - Criteria to be defined to expand eligibility to other NRAs
- Formalization of collaboration agreements with NRAs in countries with PQd vaccines for exchange of information in case of problems (quality, AEFIs, recalls, non-compliance with GMP, etc).

Confidentiality and collaboration agreements are being signed with relevant NRAs



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## **Normal and Streamlined Procedures**

#### **NORMAL**

Screening of file

**Payment of fees** 

Full review of dossier quality and clinical data

Testing of not less than 3 final lots for consistency purposes

Site audit to manufacturing facilities

**Review of UN related items** 

#### **STREAMLINED**

Screening of file

**Payment of fees** 

Review of assessment report provided by responsible NRA

Review of test results performed in NCL of producing country

Review of reports of inspections carried out by NRA

**Review of UN related items** 

Or combination of some of the above with review by PQ experts



## Features of the revised procedure What is Programmatic Suitability for Prequalification (PSPQ)

- Programmatic suitability
  - Adequacy of presentation (vials, auto-disable syringes, multidose presentations with/without preservative)
  - Stability profile suitable for countries with weak cold chain systems
  - Ensure applicability of an adequate vaccine vial monitor (VVM) type
  - Primary/Secondary packaging: Volume of cold space required
  - Remaining shelf life at time of shipment



#### **Objective of programmatic suitability (PSPQ)**

Ensure that vaccines used in low and middle income countries can be used safely and effectively, given the constraints and conditions of their immunization systems



Nicaragua, rotavirus delivery, Photo: Gates Foundation



Mali, polio campaign, Photos: WHO/Olivier Ronveaux



## **PSPQ characteristic categories**

Type of characteristic	Compliance	Deviation	
Mandatory	Prequalification evaluation proceeds.	Rejection of application for prequalification evaluation.	
Critical	Prequalification evaluation proceeds.	Referral to the PSPQ Standing Committee for review, discussion and recommendation. After consideration of the PSPQ Standing Committee advice, the vaccine may be accepted or rejected for prequalification evaluation.	
Unique and innovative	Referral to the PSPQ Standing Committee for review, discussion and recommendation. After consideration of the PSPQ Standing Committee advice, the vaccine may be accepted or rejected for prequalification evaluation.		
Preferred	Prequalification evaluation proceeds.		



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#### Vaccine characteristics that will affect pre-qualification

#### Mandatory

- Compliance is compulsory
- Failure to meet this characteristic will prevent the vaccine to be further considered for pre-qualification

#### Critical

- Compliance is also compulsory
- However, deviations in vaccine characteristics will be reviewed by the Programmatic Suitability for WHO Prequalification (PSPQ) Standing Committee
- Under special circumstances exceptions can be granted to vaccines that deviate from the critical characteristics.
- Decision can only be taken by the PQ Secretariat and will include consideration of recommendations from the PSPQ Standing Committee and consideration of topics such as public health need and access to vaccines.



## Vaccine characteristics that are unique

#### Unique (characteristics not otherwise specified)

- Are reviewed by the PSPQ Standing Committee
- May be pre-qualified if considered by the PQ Secretariat on the advice of the PSPQ Standing Committee



Examples: Nano-patches, nasal aerosols, micro-needle application, etc



#### Vaccine characteristics that are preferred (but do not affect PQ)

#### Preferred

- Are intended to indicate what WHO and national immunization programmes would want in a best case scenario and expect in the future
- Are meant to guide vaccine manufacturers during the development of the new vaccine formulations
- A vaccine not complying to preferred characteristics would not be prevented to be further reviewed for pre-qualification
- However with time, a preferred characteristic may in future revisions be deemed to become critical



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## **Thermostability**

#### Applies to all vaccines

The vaccine or any component presented for prequalification should not require storage at less than -20°C (WHO EPI).

#### • Why?

 National programmes will be unable to maintain a cold chain that requires extended deep freezing storage, even at national levels.



MANDATORY

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# Thermostability / stor

Applies to all vaccines

- The vaccine presented for prequalification should not require storage below +2°C for longer than 6 months (WHO/IVB/06.10)
- Why?
  - Moving away from negative cold storage space, simplifying the cold chain
  - OPV only vaccine that <u>requires</u> negative storage



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## Materials, primary and secondar Cockaging and injection material

Applied to all vaccines

 The vaccine presented for prequalification should be packaged in materials that can be disposed of appropriately in the field using standard procedures (e.g., pit burning and burying, low temp incinerations. etc.) (WHO EPI).

## • Why?

- Environmental concerns
- Ability to dispose of vials / syringes safely



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# Preferred Vaccine Characte Apics

Characteristic	Value
Thermostability / storage	Storage of vaccines and diluents possible at temperatures above +8°C, especially for freeze sensitive vaccines
Process of preparation & administration	Vaccines in ready to use formats; For multi-component vaccines, a short and simple preparation process
Dose volume, oral	Smaller and standardized volume



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## **Timelines**



- Current procedure: 12 months without counting clock stops
- Streamlined procedure: not yet defined as experience with use is required. Expected not more than 6 months
- Article 58: Expected 2 months after scientific opinion



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## Timelines may vary significantly depending on



- Interest of the manufacturer to get the vaccine PQd quickly (longer when first in category for UN)
- Need to perform additional trials or introduce corrective actions
- Experience with PQ. New manufacturers take longer than manufacturers with existing PQd vaccines.



## Why is Vaccines PQ important for manufacturers?

- Gives access to the United Nations market
- Considered as a seal of quality and required by other or curing agencies: MSF, DANIDA, JICS, etc
- Also required by many self-procuring countries
- Stringent process that will foster in manufacturing facilities
  - Reaching international standards
  - Strengthening GMP and QMS
  - Krengthening clinical trial design and performance
  - Strengthening pharmaco-vigilance systems
- Sustain regulatory capacity and expertise



## **Common issues faced by manufacturers**

- Difficulty to respond to questions raised in the report of PSF
- Testing methods do not comply with WHO recommendations or are not fully developed and validated
- WHO GMP standards are not met
- QMS/QA is weak
- Pharmaco-vigilance system is not developed



## **Common issues faced by manufacturers**

#### TRIALS CONDUCT

 Insufficient documentation proving that the trials were conducted after approval by ethics committees

#### DATA PROVIDED

- Incomplete or no clinical development plan
- Lack of pharmacovigilance or risk management plan
- Poor quality trial reports with insufficient and/or contradictory information
- Clinical trial data produced with a different formulation than the one intended for marketing and for distribution to UN agencies, without proper bridging
- Small database, mostly (but not only) from the safety perspective



## **Common issues faced by manufacturers**

#### DATA PROVIDED

- Immunogenicity determined with the use of commercial and/or inhouse non-validated tests
- Insufficient follow-up to determine duration of protection
- Lack of data in target population(s) that might receive the vaccine if prequalified, when such data are needed
- Lack of data on co-administration of other vaccines
- Only immunological tests proposed when efficacy should be determined
- No post-marketing surveillance data from country of manufacture because the vaccine is produced for export only
- Poor quality post-marketing surveillance data because of lack of adequate pharmacovigilance system (manufacturer's and/or country NRA/MoH's)



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## **Support provided to manufacturers**

- Procedure published on the WHO website together with other supporting documents
- Notes for guidance published based on needs expressed by manufacturers
- Meetings with WHO (with or without NRA participation) recommended before submission, even better during vaccine development. Meetings also encouraged during the PQ process (if needed)
- Specific PQ briefing workshops for manufacturers



## Thank you



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