

Update of the procedure for WHO vaccines prequalification

by Dr. Nora Dellepiane,

Manager Vaccines Prequalification Programme

Prequalification Stakeholders meeting

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Outline of presentation

- **Introduction to the vaccines Prequalification Programme**
- **Rationale for revising the procedure**
- **Scope of the revision**
- **Revision Process**
- **Main changes introduced**
- **Timelines for implementation**

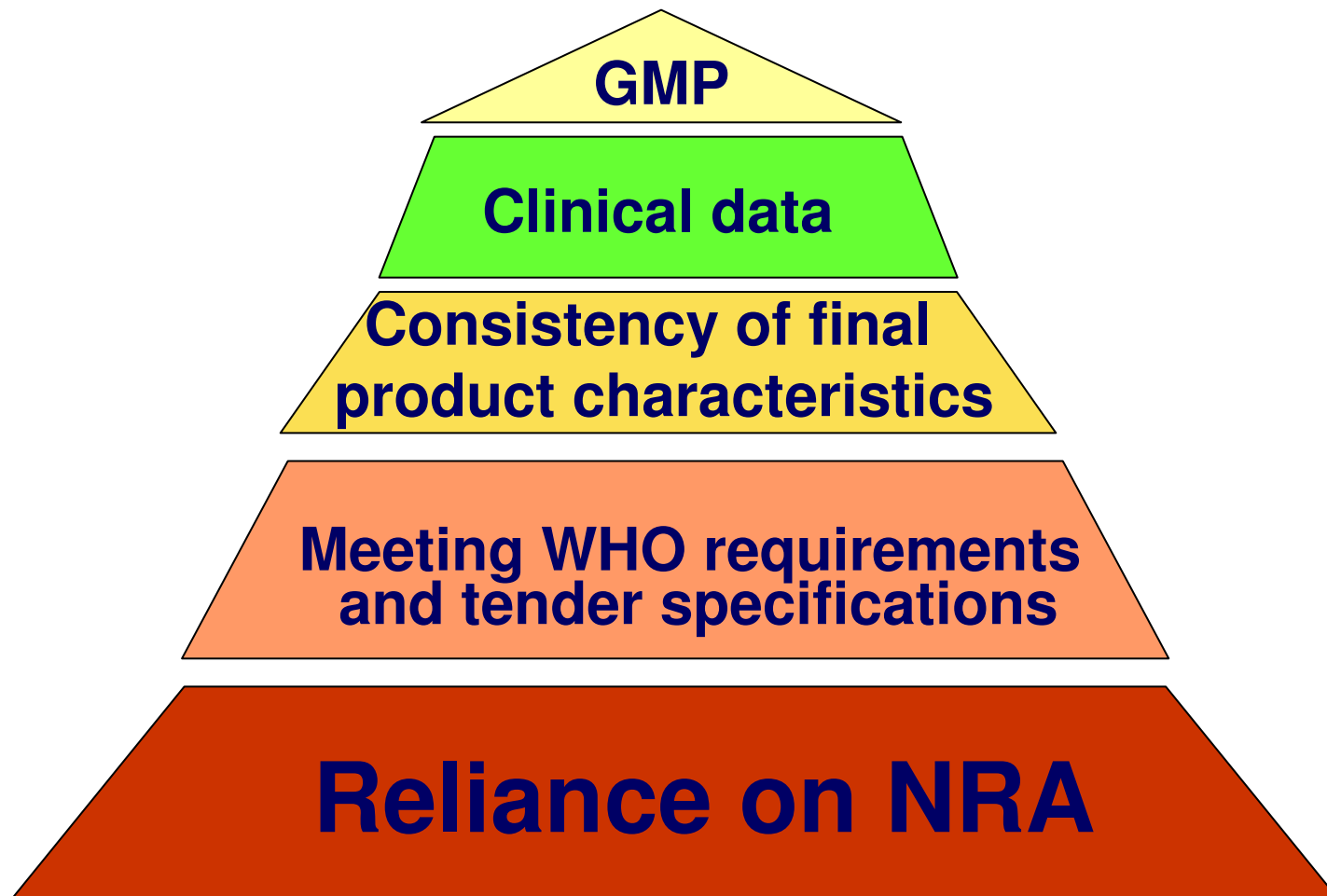


Purpose of WHO vaccines prequalification programme

- 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



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**



Pre- conditions for PQ evaluation

- **Vaccine is licensed/registered by the responsible NRA (Scientific opinion by EMA accepted)**
- **WHO guidelines/recommendations 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)**



Added value of the PQ procedure (1)

What is different in the PQ procedure from the Marketing Authorization evaluation?

- **Ensure that vaccine meets WHO requirements and the United Nations tender specifications**
- **Ensure the relevance of the available clinical data to the UN target population**
- **Immunization schedules and dosage compatible with those used in National Immunization Programmes in developing countries**
- **Feasibility of co-administration with other vaccines administered at same time in NIPs**
- **Stability profile: Cold chain requirements/ suitability for use under field conditions, shelf life and remaining shelf life at time of shipment**
- **Packaging: Volume of cold space required, primary and secondary packaging characteristics**
- **Ensure applicability of an adequate vaccine vial monitor (VVM) type**



Added value of the PQ procedure (2)

What is different in the PQ procedure from the Marketing Authorization evaluation?

- **Suitability of presentation (vials, ampoules or prefilled auto-disable syringes)**
- **Applicability of WHO Multidose vial policy: WHO Policy Statement- The use of opened multi-dose vials of vaccine in subsequent immunization sessions (WHO/V&B/00:09)**
- **Adequacy of information on labels for vials and boxes and package inserts: all relevant information is stated, insert reflects product characteristics and does not contradict model inserts and WHO policies. Availability in all required languages**
- **Tertiary packaging: Vaccine boxes for international shipments are prepared according to the WHO shipping guidelines and are properly validated. "Guidelines on International Packaging and shipping of vaccines (WHO/IVB/05.23)**





Vaccines prequalified by WHO: Status 2010 (assured quality)

15
*industrialized
country mfrs*

- ✓ Australia
- ✓ Belgium
- ✓ Canada

- ✓ Denmark
- ✓ France
- ✓ The Netherlands

- ✓ Germany
- ✓ Hungary

- ✓ Italy

- ✓ Japan
- ✓ Rep. of Korea
- ✓ Switzerland

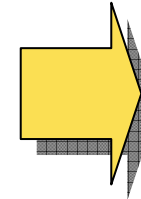
- ✓ Sweden
- ✓ United Kingdom
- ✓ USA

8
*emerging
economy
country mfrs*

- ✓ Brazil
- ✓ Bulgaria

- ✓ Cuba

- ✓ India
- ✓ Indonesia
- ✓ Russia
- ✓ Senegal
- ✓ Thailand



29
manufacturers

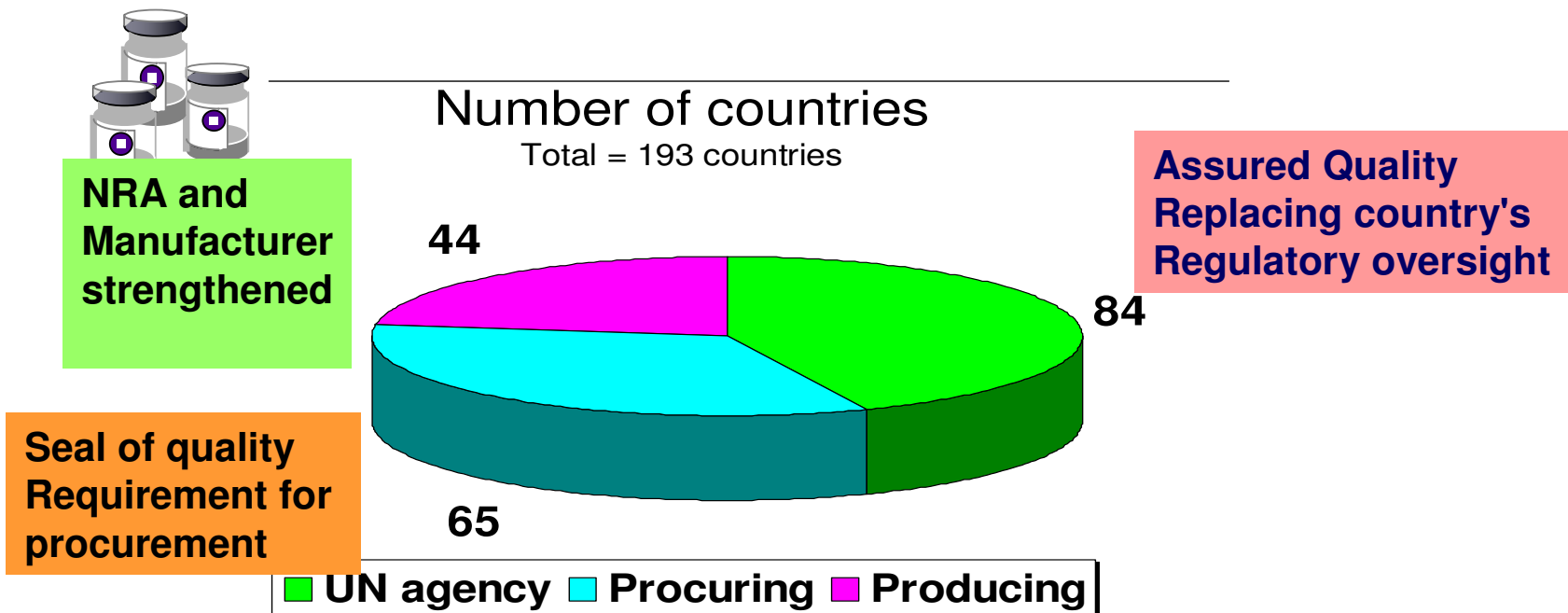
115 pre-qualified
vaccines

used in 124
countries

64% total
population

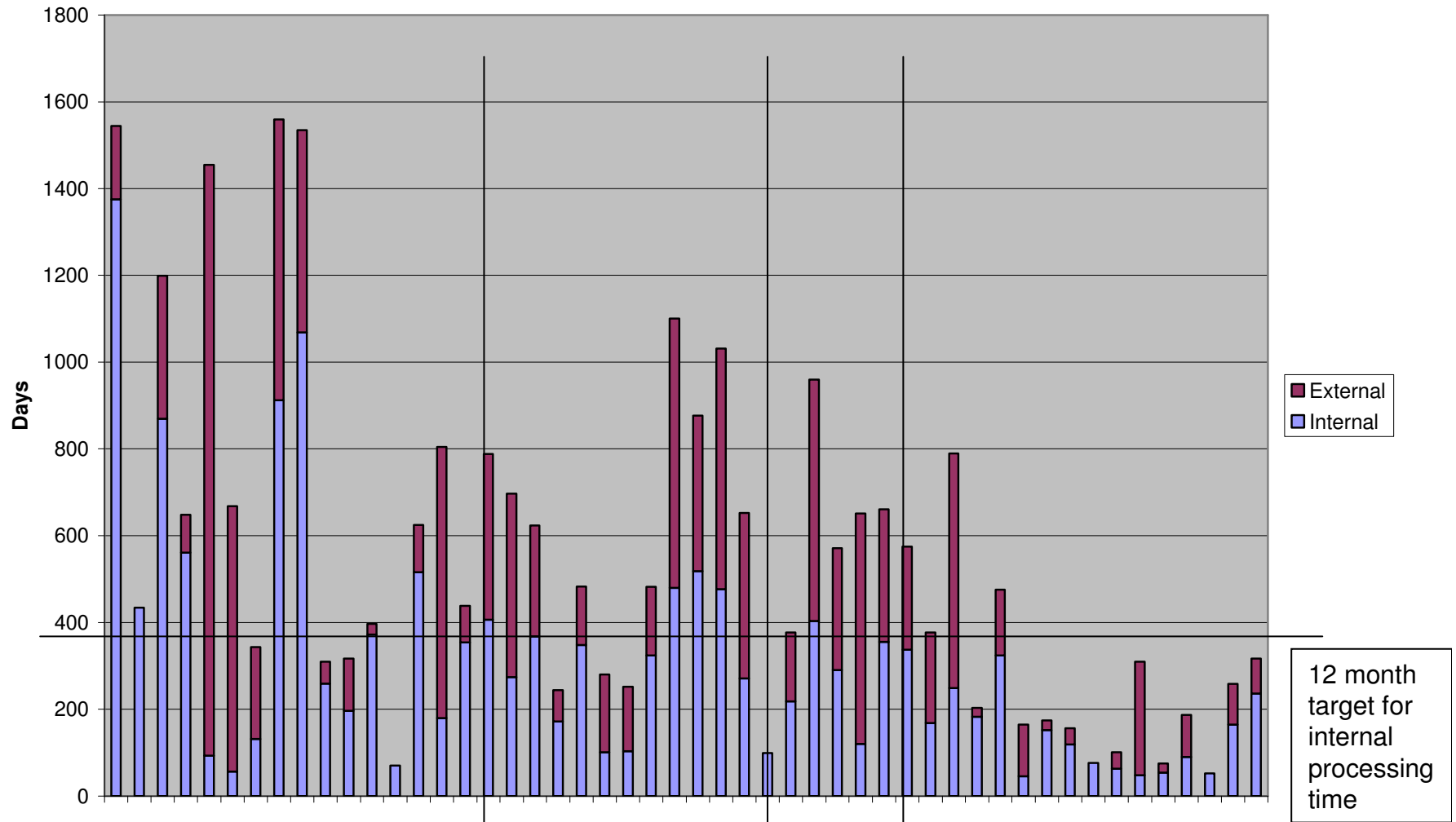


Vaccines Prequalification- Impact



4) PQ performance

Pre-Qualification Process Time
(completed applications)



Compliance with PQ target timeframes

- **Target timeframe of 12 months internal processing has significantly improved between 2007 and 2009 (data for 2010 under evaluation) due to increased resources**
- **Major reasons for failure to meet timeframes are:**
 - 1. Vaccine characteristics deviate significantly from those needed in national immunization programmes in developing countries and no specific procedure in place to deal with the deviation (no preservative or not enough, pre-filled non auto-disable syringes, etc)**
 - 2. Applicant is new to the PQ system and does not meet expectations up front, thus requiring time to adjust in order to meet requirements**
 - 3. Vaccine is not high priority for manufacturer taking long time to submit responses to questions (seasonal flu before pandemic)**
Therefore, need to develop a tracking system to reflect clock stops and timeframe taken by WHO and by applicant Information to be uploaded on the website



Rationale for revising the procedure (1)

CHANGING LANDSCAPE IN THE VACCINES ARENA

- **Expectations about the PQ programme significantly increased in the last five years**
- **Rich pipeline of novel vaccines**
- **Large number of manufacturers working in vaccine development**
- **Innovative financing mechanisms accelerate access to greater diversity of vaccines**
- **Number and diversity of vaccines offered for prequalification has increased, trend expected to continue in coming years**



Rationale for revising the procedure (2)

CHANGING LANDSCAPE IN THE VACCINES ARENA (2)

- **Increased complexity of products, availability of new technologies, multiple production sites and partnerships**
- **Manufacturers from countries such as China and Thailand are emerging as important new clients**
- **Regional priorities need to be addressed**
- **Need to better define programmatically acceptable product characteristics**
- **While expectations and demand have increased, PQ resources likely to remain stable**
- **Regulatory challenges**



Resources

- **Small secretariat at WHO/HQ**
- **GMP experts from NRAs collaborating with WHO**
- **GMP independent consultants hired by WHO**
- **Quality assessors mostly from NRAs/NCLs collaborating with WHO**
- **Clinical assessors from NRAs collaborating with WHO**
- **Independent consultants with expertise in clinical evaluation hired by WHO**
- **Contracted laboratories to perform testing activities**



Scope of the revision

- **Technical**
- **Policy**
- **Communication**



Revision Process (1)

- WG1: Programmatic Suitability of Vaccines**
- WG2: Comparison between the different WHO PQ procedures (Medicines, diagnostics, vaccines)**
- WG3 New approaches to testing**
- WG4 Streamlining of the PQ procedure for products with CHMP positive scientific opinion**
- WG5 Establishment of maturity levels for NRAs**
- WG6 Format and contents of file
Approach to reassessments, review of updates and responses**
- WG7 Feasibility of streamlining the PQ procedure (risk based approach)**
- WG8 Regulatory oversight of vaccines manufactured in multiple sites/countries**

WHITE PAPERS



Revision Process (2)

WG1: Programmatic suitability of vaccines →

WHITE PAPER

WG2 to 8 →

WHITE PAPERS

Other policy and
Communication matters
+ points to consider for
Manufacturers and
reviewers

**SAGE's 13-15 April 2010 for
comments**

Proposals for revision

**Ad-Hoc Committee on Vaccines Prequalification
May 2010**

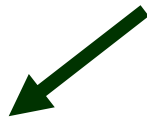


Revision Process (3)

**Ad-Hoc Committee on Vaccines Prequalification
May 2010**



Recommendations



WHO-PQ Secretariat



**Develop revised draft procedure
by 30 June 2010**



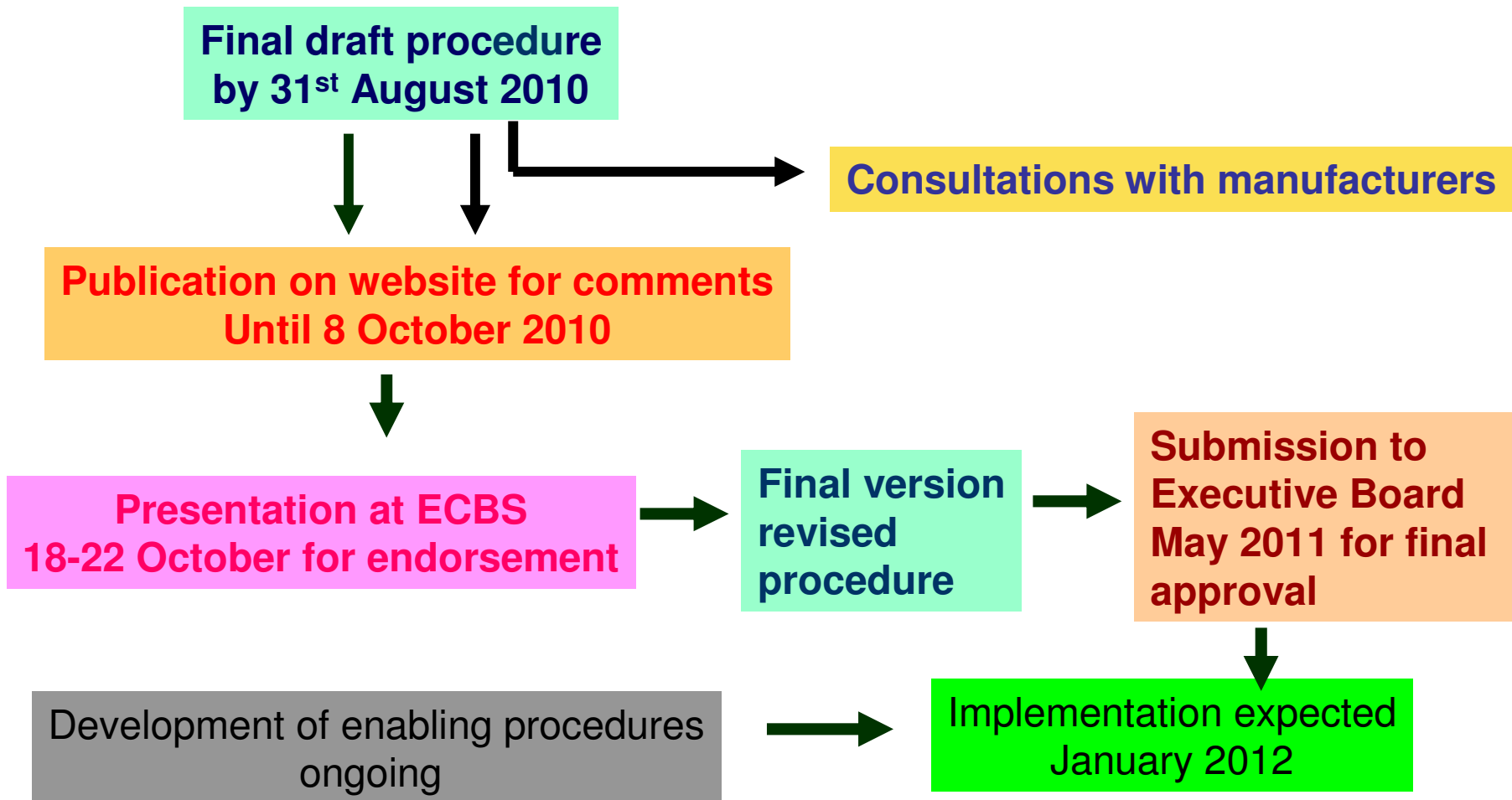
**Publication on website for comments
Until 31st July 2010**



**Final draft procedure
by 31st August 2010**



Revision Process (4)



Main changes introduced (1)

TECHNICAL

- **Development of "Points to Consider" documents to guide manufacturers and reviewers on requirements for PQ:**
 - "Clinical considerations for evaluation of vaccines for prequalification" **(finalized and published)**
 - "Environmental monitoring of clean Rooms in vaccine manufacturing facilities" **(finalized and published)**
 - "Variations in vaccine manufacturing" **(pending)**
- **Review based either on PSF or CTD type of dossiers with cross referencing to PSF format**
- **Development of procedures subordinated to the main prequalification procedure: updating of documentation to enable implementation of revised procedure (work ongoing)**
- **Development of document on acceptable product characteristics "Assessing the Programmatic Suitability of Vaccine Candidates for WHO prequalification" (Final draft pending adoption by IPAC)**



Main changes introduced (2)

POLICY

- **Establishment of rules for a risk-based approach to vaccines prequalification (streamlined procedure)**
 - Criteria and conditions for applying a streamlined procedure based on collaboration agreements with stringent NRAs (maturity levels to be established in NRA assessment programme) **(ongoing)**
 - Streamlined procedure to be established
 - Risk-based approach to reassessments **(ongoing)**
 - Risk-based approach to testing of samples **(ongoing)**
- **Prequalification pathway for vaccines with a positive Article 58 opinion**
 - Streamlined procedure to be established **(ongoing)**
- **Prioritization process **(implemented, process confirmed)****
- **Establishment of the Programmatic Suitability for Prequalification Standing Committee (PSPQ Standing Committee) **(ongoing)****
- **Establishment of Annual Product Reports system **(ongoing)****
- **Regulatory oversight of products manufactured in multiple sites to be agreed upon on case by case basis depending on functionality of the relevant authorities and willingness to take on the required functions **(ongoing)****



Streamlined review procedure

- **Based on agreement with a sNRA, the three steps of the prequalification procedure can be facilitated as follows:**
 - **Review of NRA assessment reports instead of reviewing the complete dossier, except for clinical data where separate review is required**
 - **Review of test results by responsible NRA instead of performing independent testing**
 - **Short site audit to review tender related matters instead of full flesh site audit based on inspection reports from responsible NRA**
- **Agreements with eligible NRAs (those where collaborative arrangements existed for pandemic influenza vaccines) currently being established**



Streamlined procedure in the context of art. 58

- **Evaluation by EMA of a vaccine eligible for art.58 includes WHO invited experts, PQ staff as observers and NRA representatives of target countries**
 - Evaluation covers non-clinical, clinical and quality aspects assessed against WHO recommendations.
 - Evaluation includes review of clinical data relevant to the target population
 - Evaluation includes inspection of manufacturing facilities with participation of WHO
- **Prequalification evaluation may include independent testing (if data independent from the manufacturer are not available) and review of tender specifications**



Main changes introduced (3)

COMMUNICATIONS

- Improved list of prequalified vaccines (providing more details on Pqd product) **Implemented**
- Publication of short document providing rationale for acceptance of a specific vaccine (Vaccine Product Assessment Report: VPAR) **pending**
- Publication of list of contracted laboratories **pending**
- Publication of list of products accepted for evaluation and charts of progress for each product **pending**
- Publication of updated priority list for 2011-2012 **implemented**



Main changes introduced (4)

PSPQ DOCUMENT: types of vaccine characteristics

- **'Mandatory' characteristics are those where compliance is compulsory at the time of application for WHO prequalification and must be met prior to evaluation of the PSF. PSF will be rejected if not met.**
- **'Critical' characteristics: compliance is also compulsory. However, if upon screening of the PSF a deviation is observed from the characteristic value, the PQ Secretariat will refer the issue to the Standing Committee for advice**
- **'Unique/innovative' characteristics: no mandatory compliance but referred to the Standing Committee for advice**
- **'Preferred' characteristics are intended to reflect what WHO, procuring agencies and national immunization programmes would want in a best case scenario and expect in the future; these characteristics are intended as guidance to manufacturers.**



Main changes introduced (5)

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. The vaccine may be accepted or rejected for evaluation
Innovative/Unique	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	



Main changes introduced (6)

PSPQ DOCUMENT: examples of different characteristics categories

- **'Mandatory' characteristic:**
 - The vaccine or any component presented for prequalification should not require storage at less than -20°C (WHO EPI).
- **'Critical' characteristics:**
 - For oral vaccines: The vaccine presented for prequalification should be packaged in a single component/ready to use format (WHO EPI).
 - For all vaccines: The vaccine presented for prequalification should not require storage below $+2^{\circ}\text{C}$. (WHO/IVB/06.10).
 - For all vaccines: The vaccine presented for prequalification should have a thermostability profile that will enable it to be matched to a WHO approved VVM type (VVM2, VVM7, VVM14 or VVM30) (WHO/V&B/99.18, WHO/IVB/07.04).
- **'Preferred' characteristics:**
 - For oral vaccines: smaller volumes and standardized volumes are preferred (WHO EPI).
 - For all vaccines: vaccines and diluents that can be stored for extended periods at temperatures above $+8^{\circ}\text{C}$ are preferred (TLAC).



Main changes introduced (7)

- **The application of the PSPQ requirements is prospective and not retroactive (not applicable to already PQd vaccines or ongoing evaluations)**
- **It will provide a transparent mechanism to communicate desired characteristics and to evaluate applications**
- **It will guide manufacturers and vaccine developers as to what are the desired product characteristics for vaccines to be used in developing countries**
- **Adequate timeframes will be given to allow for adjustment of already prequalified vaccines to meet the PSPQ critical or mandatory characteristics**



THANK YOU



Dr. Nora Dellepiane, Scientist WHO/IVB/QSS 4 April 2011



World Health
Organization