

***Procedure for assessing the acceptability,
in principle, of vaccines for purchase by
United Nations agencies: Revision 2010***



**World Health
Organization**

Background

Why was the revision of the PQ procedure needed?

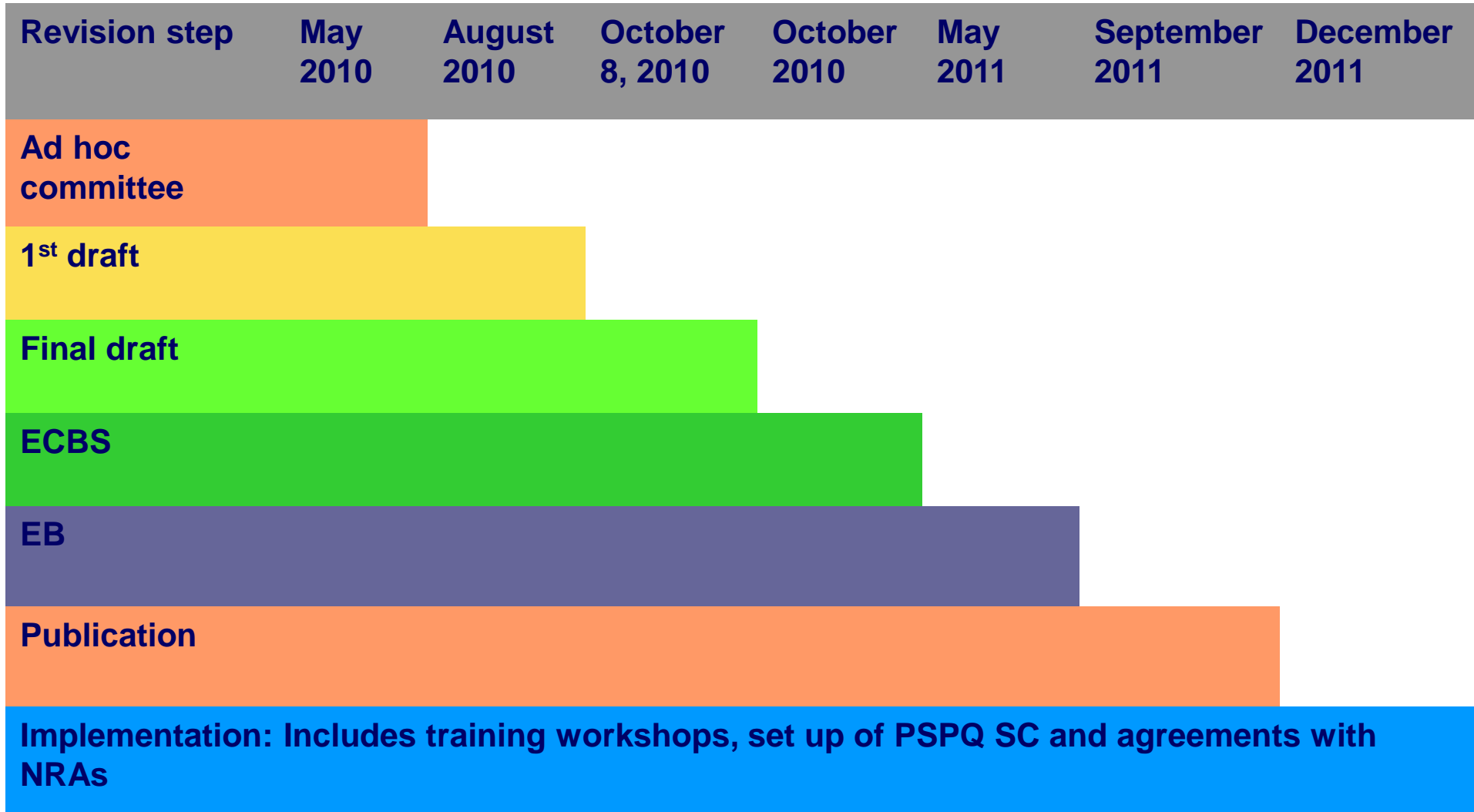
Need for revision of the PQ procedure

- **Increased number of novel vaccines and vaccine combinations available**
- **High number of vaccines in the pipeline**
- **Large number of manufacturers working on the development of new vaccines**
- **Increased complexity of products, availability of new production technologies, multiple sites, partnerships between manufacturers**
- **Increased demand for PQ evaluation likely to continue and even accelerate**
- **Need to better define programmatically acceptable product characteristics**
- **Need to develop a business plan for long-term sustainability of the PQ programme**

Revision Process



Revision Process



Purpose of the PQ: remains unchanged

Assurance that candidate vaccines:

- (a) meet the WHO recommendations on quality, safety and efficacy including compliance with WHO recommended Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) standards;
- b) meet the tender specifications of the relevant UN agency to ensure that vaccines used in national immunization services meet particular operational specifications for packaging and presentation, and are suitable for the target population, at the recommended schedules with appropriate concomitant products.

Principles: remain unchanged

- Reliance on the National Regulatory Authority (NRA) of the country of manufacture
- General understanding of the product and presentations offered, production process, quality control (QC) methods, quality system (QS) in place and relevance for the target population of available clinical data.
- Assurance of production consistency through compliance with GMP requirements and monitoring of continued compliance with specifications through testing of final product characteristics

Summary of changes



Pre-conditions for application

- The candidate vaccine is on the priority list as defined by United Nations purchasing agencies, IVB Strategic Advisory Group of Experts (SAGE), and partners.

- The NRA exercising the regulatory oversight is declared "functional" by a WHO independent team

ENDORSED

- The candidate vaccine is licensed by the NRA exercising the regulatory oversight (or given a positive scientific opinion under art. 58 by EMA)

- The candidate vaccine meets the mandatory characteristics for programmatic suitability

NEW

Steps of the procedure: Official request and response

- Application letter submitted by manufacturer to Coordinator QSS indicating main characteristics of the product, presentations offered and proposed date for submission and copied to PQ manager and NRA

- Acknowledgement of receipt and acceptance of application by email only, rejection of application informed by official letter

CHANGE

Steps of the procedure: Pre-evaluation meetings

- To be scheduled as early as possible in the vaccine development with proposed agenda sent in advance by the manufacturer, aimed at discussing product characteristics, target population, indications, regulatory pathway, etc. **CHANGE**
- Additional meetings may be held during the evaluation process as required

Steps of the procedure: Product summary file

- One hard copy and five electronic copies instead of two hard copies and one electronic copy
CHANGE
- Where PSF cross references to the Common Technical Document, CTD documentation can be e-copy only. E-copy documents should be searchable text where possible.
- Submissions received after the deadlines will not be considered for evaluation until the following review round. Submission dates remain the same

Steps of the procedure: Screening of the PSF and payment

- PSF will be screened for compliance with format and contents
- PSF will be screened for compliance with programmatic suitability of vaccine characteristics (PSPQ paper)



In case of non-compliance, mfg will be informed by letter and required to pay screening fee, a second opportunity for submission will be given without additional payment of screening fee. If rejected again, a second screening fee would be charged

NEW

Steps of the procedure: Screening of the PSF and payment

Assessment of the suitability of the vaccines for the immunization services where it is intended to be used (PSPQ paper)

- Vaccines candidates must be in compliance with the mandatory characteristics, else the submission will be rejected
- If vaccines candidates are not in compliance with the critical characteristics or a unique, novel and innovative characteristic is identified, a recommendation from the PSPQ SC is required

NEW

Steps of the procedure: Review by PSPQ-SC

- The PSPQ Standing Committee is an advisory body to the PQ Secretariat and the Director IVB constituted of experts on immunization programmes and vaccines regulation.
- The committee will review exclusively the documentation related to the specific problem to be discussed and all members will be required to sign confidentiality agreement and declaration of interest forms prior to taking up their responsibilities for WHO.
- During their review, the Committee may engage in confidential discussion with manufacturers and additional technical experts approved by WHO and the manufacturer.
- Maximum timeframe for review is 3 months, screening process is put on hold

NEW

Note: Under special circumstances, when there is limited access to a vaccine of public health importance, exceptional considerations will be made regarding vaccine candidates that are non-compliant with the critical characteristics. This decision can be made by the IVB Director and PQ secretariat with consideration of the recommendations of the PSPQ



Steps of the procedure: PSF evaluation

- Review timeframe is 3 months, report sent to manufacturer
- Clock stopped awaiting responses to questions
- Responses to be received in "one package" (one hard copy and 5 electronic copies), otherwise review (and clock) will start only when all outstanding questions have been addressed **ENFORCED**
- Timeframe for review of complementary info is 3 months

Steps of the procedure: Initial testing of vaccine samples

- Appropriate number of samples from 3 to 5 lots formulated from consecutive bulk lots. SLP and SOPs for testing, biological reagents and reference materials are provided by the manufacturer to WHO to be shared with the labs for validation purposes.
- Samples should be representative of the product to be supplied to UN and manufactured at commercial scale.
- Usually samples are tested for potency or other relevant tests. If applicable the relevant method should be transferred from the manufacturer to the contracted laboratory through WHO.
- Timeframe for testing is 3 months **FURTHER CLARIFIED**
- The list of contracted laboratories will be made public, but not the specific laboratory in charge of testing specific samples

Steps of the procedure: WHO site audits

Purpose and scope remain unchanged, only name changed to site audits rather than site visits

Steps of the procedure: Outcome of the evaluation

- Letter to UN agencies informing of the prequalification advising on compliance of the vaccine with the WHO requirements and the tender specifications and role of the NRA in certifying this
 - Copy to GAVI (for AMC eligible products)
 - Copy to manufacturer, NRA and NCL
 - Copy to relevant Regional and country Offices
 - Copy to IVB management

Considerations for streamlining the PQ procedure (New section)

Proposed streamlined procedure based on enhanced reliance on the oversight performed by the responsible NRA, when the NRA exhibits a high level of performance of WHO's six recommended regulatory functions and exercises full regulatory oversight of any given vaccine.

- Revision of NRA assessment tool planned June 2011, meanwhile, interim process to select NRAs
- Applied to:
 - a) Vaccines with MA/licensing granted by eligible NRAs
 - b) Vaccines with positive scientific opinion issued by EMA

CHANGE

Special considerations for fast-track procedure

This procedure is applicable to licensed vaccines (marketing authorization available) that are part of the routine immunization programmes or those that are used only as an emergency response but not applicable to novel vaccines not yet introduced and can be considered in the following situations:

- An acute shortage^[1] of a vaccine that puts at risk the global supply of routine immunization programmes.
- An emergency situation or outbreak of a disease for which there is no prequalified vaccine, or its availability is not sufficient and an additional source of the same vaccine is required.

^[1] As agreed with UN purchasing agencies and other partners.

Special considerations for accepting submissions before the license is granted

SECTION DELETED

Submissions will not be not accepted anymore before the license is granted

CHANGE

Submission of vaccines manufactured in multiple sites or countries

- It is a pre-condition to any submission that the NRA responsible for the regulatory oversight must be functional as assessed by WHO. Functionality needs to be sustained

- Responsibility for overseeing manufacturing of different production steps should be shared between the relevant authorities

It is clearly indicated that the regulatory oversight should be ensured throughout the manufacturing process by a functional NRA

ENFORCED

Submission of vaccines manufactured in multiple sites or countries (2)

- For OPV vaccines, the bulk material must have been evaluated as part of a vaccine already prequalified
- The use of totally unrelated (third party) NRA would not be acceptable. WHO can make a case by case decision when an agreement between NRA's for a specific product is established.

CHANGE



Obligations after the PQ is granted (ex- Supply section)

The manufacturer shall inform WHO/IVB/QSS of changes/variations that must be notified or submitted to the NRA in the following cases: (a) may result in a change of safety and/or efficacy of the vaccine, or (b) change the basis of the regulatory approval by the NRA.

If the manufacturing country regulations do not require approval by the NRA of changes/variations that fall under categories (a) and (b) stated above, WHO shall be informed of the proposed changes before implementation on products supplied to United Nations agencies.

- If reliance on responsible NRA, an annual summary of changes would be sufficient. If reliance is not established, changes/variations that fall under a) or b) above, must be approved by WHO. Other changes can be reported on annual basis.

CHANGE

Annual reporting (New section)

Description of variation	PSF Ch/section	CTD X-ref (where appropriate)	Responsible NRA			WHO prior approval date (where required) Or WHO notification date (as applicable)‡
			Prior approval date	Date of acknowledgment of notifiable change†	Self-assessable under national law or not applicable to national registration [☑ if required]	

Reassessments

- PQ status is maintained until action is taken by WHO to revoke it
- The frequency, scope and need of reassessment will be based on quality risk management principles

Risks based approach rather than at regular intervals as before

CHANGE

Monitoring of compliance with specifications

Targeted testing programme

Manufacturers should commit to keep adequate number of retention samples for testing by WHO contracted laboratories upon request

Monitoring vaccine quality complaints or AEFIs from the field

- In case of vaccine quality complaints, WHO will conduct an investigation and may perform independent testing after review of the relevant documentation
- In case of complaints from the NCLs in the receiving countries, review by WHO of the testing results and related documentation from these labs is needed before arbitration testing is commissioned
- In case of serious AEFIs or whenever WHO consider necessary WHO will conduct an investigation according the established procedure

Handling of OOS/inconsistent results between laboratories (New section)

- In the case of inconsistent results by the two WHO contracted laboratories, WHO may require testing of the vaccine by a third laboratory
- WHO may convene an ad hoc committee to assess the combined results and make a recommendation to WHO
- Representatives from the WHO contracted laboratories may take part in this committee

NEW

Costs

- Fees (screening, initial evaluation of candidate vaccines and annual maintenance fee) are kept on a separate list available in the website and remain unchanged

No conflict of interest

- New declaration of interests for WHO experts attached as Annex 5

Supporting documents

- **Points to Consider document environmental monitoring of clean rooms in vaccine manufacturing facilities developed with collaboration of manufacturers during Chiang Mai meeting, February 2010. To be posted on the website for public comments soon**
- **Points to consider on clinical considerations for evaluation of vaccines for prequalification developed with collaboration of manufacturers during Chiang Mai meeting, February 2010. Currently posted on the website for public comments**
- **Document on variations to the prequalification file, currently under preparation after consultation with manufacturers during Chiang Mai meeting, February 2010**
- **Current draft of the revised procedure resulted from papers produced by eight working groups that were presented to the Ad Hoc Committee on Prequalification in May 2010, plus the recommendations of the said committee, plus two rounds of public comments**



IMPROVEMENTS

- Increased reliance on regulatory oversight exercised by robust NRAs i.e. better use of PQ resources
- Better fit with industry and UN procuring agencies and other partners' needs (e.g. avoid duplication, potential for time reduction of PQ process, more guidance for industry)
- Clearer rules (PSPQ process, clinical guidance document)
- Increased transparency (more information on the website - list of WHO contracted labs, summary of decision for granting PQ)

Acknowledgements

- Groups of experts in GMP and clinical, Chiang Mai Meeting
- Manufacturers representing DCVMN at Chiang Mai meeting
- Members of the Ad Hoc Committee on Vaccines prequalification
- WG1: Assessing the programmatic suitability of vaccine candidates for WHO prequalification
- WG2: Comparison of Prequalification Programs
- WG3: Revised approaches to testing final product characteristics
- WG4: Streamlining the prequalification procedures for products with EMA/CHMP positive scientific opinion
- WG5: WHO assessment of vaccines regulatory system: Proposal for establishment of maturity level concept
- WG6: Requirements for Product Summary File submitted for prequalification. Initial evaluation and reassessment and requirements for annual report for prequalified vaccines
- WG7: Streamlining the prequalification procedure: Consideration of a risk-based approach
- WG8: Regulatory oversight of vaccines manufactured in multiple sites/countries
- WHO Secretariat
- PQ secretariat
- Ms. Emma Uramis, WHO STC

