Informal consultation with the ad hoc committee on vaccines prequalification for the revision of the procedure for assessing the acceptability, in principle, of vaccines for purchase by UN agencies

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Summary of recommendations from the ad hoc committee on vaccines prequalification

Session 1 The WHO prequalification procedures

The first presentation was a briefing on the current vaccines prequalification procedure and its rationale for revision.

The ad hoc committee was presented with the comparison of WHO prequalification programmes and noted that the flow of the different procedures is similar and the major differences are vaccines' reliance on functional National Regulatory Authorities (NRAs), terminology used for assessing Good Manufacturing Practices (GMP) compliance in manufacturing facilities, web information and fees.

Discussion was around the following issues:

- Acceptance of Product Summary File (PSF) format as default for data submission or adoption of the Common Technical Document (CTD) as required by Medicines prequalification programme.
- Use of term "site inspection" by Pharmaceuticals and Diagnostics while "site visit" by Vaccines.
- Providing additional information on the web concerning prequalified vaccines.
- Prerequisite for regulatory oversight by functional NRAs.
- Feasibility of streamlining the prequalification (PQ) procedure for vaccines manufactured under the oversight of functional/mature NRAs.
- Discontinuation of parallel review with national licensure.

The ad hoc committee made the following recommendations:

- PSF format should be maintained, it is a concise document that fulfils WHO requirements and is easy to review by assessors; CTD is accepted with appropriate cross references to PSF.
- Terminology between the WHO prequalification projects should be harmonized perhaps based on International Standards Organization (ISO) guidelines. The term "site audit" should be used instead of "site visit".

The ad hoc committee supported the idea of making a public assessment report however expressed its concern on the additional work for WHO. This discussion was deferred to the specific session.

The ad hoc committee emphasized that vaccines are biological products, more complex products than medicines, therefore require functional NRA to exercise the regulatory oversight of prequalified products. This topic was discussed in detail in the specific session.

The ad hoc committee supported, in principle, the idea of streamlining the PQ procedure for vaccines manufactured under the control of functional/ mature NRAs. The detailed discussion was held in another session.

Based on the unsatisfactory experience accumulated to present with the use of the existing provision for accepting submissions before national license is granted (i.e. for priority products), the ad hoc committee concluded that such provision should not be kept. However, provisions for implementing a fast-track procedure for evaluation of vaccines in emergency or outbreak situations should be kept as is.

Session II Technical Updates

The ad hoc committee was brought up to date on the process for development of the following notes for guidance:

- Clinical considerations for evaluation of vaccines for prequalification
- Environmental monitoring of clean rooms in vaccine manufacturing facilities
- Variations to the prequalification file.

The ad hoc committee discussed the process for development of guidance documents intended to provide technical clarifications to already established standards, especially GMP, and other standards related to vaccines; whether such documents should be published on the WHO website for further review; and the process for regular updates to ensure they become living documents.
The ad hoc committee stated that these guidance documents should provide specific technical clarification and should not be in contradiction with existing standards. These

should be published for general use, since they would have value for regulators and manufacturers in general, and not just for prequalified vaccines.

The committee also pointed out that there is no environmental monitoring guidance available specifically for vaccines, therefore such guidance is required. However, as this document will establish a new standard, then review by a WHO Expert Committee will be required.

The ad hoc committee made the following recommendations:

- develop written procedures for establishing this type of document;
- call these documents "Points to consider" instead of "Notes for guidance";
- publish them as drafts in the web for further comments;
- that the points to consider on environmental monitoring (EM) required further drafting, including review by the WHO standards setting team from the medicines department (QSM) before publishing as a draft document in the website;
- send the points to consider on EM to the relevant Expert Committee for approval.

The ad hoc committee also stated that only the document development process was endorsed and not the guidances' content as they were not submitted for consideration by the committee.

The ad hoc committee was presented with the proposed changes to information requirements for product summary file submitted for prequalification, for initial evaluation and at reassessment, and requirements for annual report for prequalified vaccines.

The ad hoc committee supported the following proposals made by the working group:

- with minor modifications, changes to the content and format of PSF;
- for initial assessment one e-copy and one hard copy of the PSF should be submitted. For CTD one e-copy only;
- for reassessment only electronic copy is needed.

The ad hoc committee also recommended:

- *reconsider the provisions for frequency, scope, and the need for reassessment based on quality risk management principles;*
- strengthen the annual reporting, as this may allow to waive the reassessment
- include complaints as part of the annual report.

The ad hoc committee was asked to consider the suitability of the proposed approaches for testing (See table 1 in Annex 1) during initial evaluation, including actions in case of complaints/adverse events following immunization (AEFIs) and in case of out-of-specifications (OOS) /failures.

The ad hoc committee expressed concern on the targeted testing workload for the QSS team and questioned whether this can be waived or reduced if done by stringent NCL and based on satisfactory results over time. The committee also highlighted that trending of data may show more than testing.

The ad hoc committee made the following recommendations on the proposed testing approaches:

- There should be more reliance on the NRA/NCL in producing countries so long as method transfer is validated and implemented.
- Less testing during the initial evaluation of vaccines submitted for prequalification should be performed by independent WHO contracted laboratories; some tests now are product specific so only are undertaken in the producing/releasing countries.
- NRA/NCL should share testing information including trends analysis (if applicable) with WHO, with agreement of manufacturer, and then further testing during the initial evaluation of vaccines submitted for prequalification might not be required. Targeted testing programme to monitor continued compliance with specifications should be maintained.
- Need for appropriate training programmes.
- Develop a detailed procedure on how investigations of OOS should be conducted.
- Need for procedure stating when WHO supports testing of vaccines following AEFIs.

Session III Regulatory oversight of PQ vaccines

The ad hoc committee was asked to endorse the vaccines PQ approach of reliance on functional NRAs as a pre-condition to accept applications and also a proposal to formalize information sharing agreements between WHO and NRAs of countries with prequalified vaccines.

The ad hoc committee endorsed the need to rely on functional NRA to accept submissions for prequalification and made the following recommendations:

- Reliance on functional NRAs should depend on regulatory capacity/maturity level and dealing with less mature NRAs requires more attention.
- Formal agreements with functional NRAs should be established, taking into consideration that a "one-size fits all" approach may not be appropriate due to legal differences between countries.

The ad hoc committee was asked to consider whether the proposed approach to maturity level performance of NRAs (based on indicators) should be tested. Recognizing that the maturity level concept will take some time to implement, the committee was also asked to endorse an interim solution in order to enable PQ to work on streamlining the prequalification procedure as soon as possible.

The ad hoc committee concluded that a performance component is needed in assessment of NRAs *and suggested to consider the feasibility of using the outcome of other assessment systems currently in place.*

The ad hoc committee made the following recommendations on the proposed approach to maturity levels:

- test the maturity level approach;
- use the term functionality instead of maturity level. Explore new performance indicators to implement the functionality approach;
- consider an indicator on how NRA deals with exporting products;
- add indicators where clinical trials are undertaken outside the country;
- as an alternative to maturity level approach and while maturity level indicators are developed, an interim solution will be applied based on the proposal made by working group 7 (See Annex 2).

The ad hoc committee was asked to consider proposals to ensure that the regulatory oversight of vaccines manufactured in multiple sites/ countries was acceptable for PQ purposes. Five cases were used as examples, where more than one country is involved in the production of a vaccine, to reflect the complexity of regulatory scenarios presented to the PQ group.

The ad hoc committee expressed concern regarding the difficulties to meet post marketing surveillance commitments and AEFIs in vaccines manufactured in multiple sites/countries. Specific arrangements between national regulatory authorities and PQ would be needed.

The ad hoc committee made the following recommendations regarding vaccines manufacturing in multiple sites/countries:

- ensure the regulatory oversight exercised for the product covers all required aspects;
- perform a case by case analysis;
- consider the feasibility of using an "unrelated"[1] NRA to provide regulatory oversight of a product. However the committee stressed that such approach would not be straight forward since the said authority would have to take the "full" regulatory responsibility including lot release for UN purposes, regular inspections, monitoring of variations, etc. In addition, an agreement with the manufacturer would have to be established, as well as, agreements with the NRA of producing country would be needed.

[1] An "unrelated" NRA can be any NRA which does not currently exercise the regulatory oversight for any regulatory function regarding a specific product.

Session IV Policy updates

The ad hoc committee was presented with the proposal made by the working group in charge of assessing the programmatic suitability of vaccines for WHO prequalification. This proposal outlines characteristics that define whether a vaccine is suitable for the immunization services and propose a process for reviewing these characteristics and deciding if candidate vaccines meet the programmatic suitability.

The ad hoc committee endorsed the proposed mechanism and noted that it would increase transparency. The ad hoc committee also endorsed the establishment of a standing committee to review deviations from the defined critical characteristics.

The ad hoc committee was briefed on some considerations about the future directions of prequalification and was asked to consider a proposal for streamlining the prequalification procedure using a risk based approach.

Discussions were around the following issues:

- The rationale for a risk-based approach based on the likely increased number of PQ applications and associated increase in workload for maintenance of PQ.
- Criteria to streamline work based on increased reliance on an NRA.
- 'Similarity of review' between WHO and the NRA, as a criterion for reliance on an NRA.
- Mechanisms to establish "similarity of review" such as considering evaluation of three vaccines per NRA both viral and bacterial and/or live and inactivated and/or combination / adjuvanted vaccines from different manufacturers, if feasible.
- Suitability of retrospective evaluation of an NRA to establish "similarity of review".
- Election for streamlining based on all NRAs meeting WHO criteria or those meeting WHO criteria the longest, or use of another criterion e.g. number of prequalified vaccines.
- Acceptance of reliance on an NRA includes waiving all or some the steps of the PQ procedure (PSF evaluation, testing and site audit).
- Completeness of PSF and all aspects related to the UN target population, such as clinical data, stability, packaging materials, shipment validation, programmatic aspects, still checked by WHO.
- Considering parameters like manufacturers' experience, track record of the manufacturer and vaccine type as an additional or alternative mechanism to introduce a risk-based procedure.

The ad hoc committee endorsed the proposal for streamlining the PQ procedure as the projected workload using current procedures is not sustainable.

The ad hoc committee made the following recommendations:

- Streamlining the PQ procedure should be based only on NRA's regulatory capacity.
- Increased reliance on a functional NRA is endorsed but further definition of how this will be done is needed; in the meantime an interim procedure should be pilot tested.
- For the interim procedure, three different types and recently licensed vaccines should be evaluated depending on what is produced in the country.
- *The concept of "similarity of reviews" may not be a realistic approach, and it was recommended instead to start with those NRAs with established regulatory capacity and to perform a joint review (the NRA and WHO) of the process followed by the NRA including the critical elements taken into consideration to grant the license of three vaccines recently licensed.*
- *The committee recommended that for those NRAs where reliance was conferred for streamlining the procedures for prequalification of influenza vaccines, an additional evaluation step would not be required.*
- WHO should in any case review clinical data relevant to the UN target population and specific aspects related to UN tender specifications.

The ad hoc committee considered proposals for alignment of EMA article 58 and WHO vaccine PQ procedures, as well as, other steps in the evaluation process where EMA and WHO/PQ might interact.

The ad hoc committee made the following recommendations:

- EMA article 58 and WHO vaccine PQ procedures should be aligned as proposed.
- EMA Article 58 should be used as a model where other regulatory authorities are considering establishing processes to undertake assessments for products for use in a global context.
- Increased communication is needed on EMA Article 58 to address perceptions about the quality of vaccines evaluated under this procedure. Examples include opportunities to communicate the process through WHO Regional Committee meetings; immunization program manager meetings and the WHO SAGE. The aim would be to target users of products evaluated through this procedure, not just regulators.

Session V Communications and transparency

The ad hoc committee discussed proposals to increase communication and transparency, specifically a new webpage and developing Vaccine Public Assessment Reports (VPARs).

After discussing the following items:

- Posting in the website the information listed below:
  - new vaccines added to the PQ list
  - recalls of batches from prequalified vaccines
  - quality problems detected in prequalified vaccines ("warning letters")
  - rejection of applicants and reason
  - VPARs for prequalified vaccines.

- Request manufacturer to supply draft Summary of Product Characteristics (SPC) in PSF.
- WHO assessors should add information on global use and acceptability criteria.

The ad hoc committee made the following recommendations:

- The WHO list of prequalified vaccines should be kept updated and delisting of a vaccine should be highlighted.
- Handling communication on recall or temporary hold of batches from prequalified vaccines should be included in agreements with NRAs. Identify new mechanisms to publish information on recalled batches.
- Publicize information on batches of prequalified vaccines that are put on temporary hold pending further investigation, but ensure that this information is updated when outcomes of investigations are known.
- Do not publicize rejection of applications, since such a decision may have nothing to do with product quality but, for example, that an application does not meet UN specifications.
- VPARs for prequalified vaccines may be posted in the website but the significant workload that it demands was highlighted.
- *A less resource demanding and acceptable alternative to the VPAR would be to include a page in the new list of prequalified vaccines that would provide the basis for the prequalification of the specific vaccine. In addition a link should be established to public assessment reports by the NRA when available.*

Endorsement of rules for prioritization process

The ad hoc committee was presented with the current rules for the process to prioritize WHO PQ workload, and was asked to endorse and consider ways to improve them.

The ad hoc committee endorsed the current rules for prioritization and recommended to consider interaction with GAVI as part of the process.

Pros and cons of (a) a regional PQ process and of(b) decentralization of some functions

During the closed session with the ad hoc committee a brainstorming to discuss potential pros and cons of moving towards (a) a regional PQ process and (b) decentralization of some functions of the PQ procedure was held.

The ad hoc committee considered the following pros and cons:

Pros:

- a regional PQ process would allow region-specific initiatives, such as reliance on "reference NRAs" to be recognized;
- decentralization provides an option to manage an increasing workload in the context of difficulties to increase staff in HQ;
- AEFI investigations are managed by regional office staff, so other functions such as site audits or clinical trial review could be decentralized too.

Cons:

- introducing a regional PQ process in parallel with the global process increases the risk that PQ will not be done to a single standard;
- a regional PQ process would duplicate resources, since a regional PQ secretariat would need to be established. Would need feasibility study to determine the resource requirements;
- regional tools to assess an NRAs, as envisaged by one region, must first be assessed for alignment with the global NRA assessment tool ;
- normative requirements for PQ must be centralized and so managed in HQ.

Conclusion: The PQ procedure should be kept centralized although some functions may be decentralized.

These recommendations were prepared based on the notes taken by the rapporteurs of the "Informal consultation with the ad hoc committee on vaccines prequalification for the revision of the procedure for assessing the acceptability, in principle, of vaccines for purchase by UN agencies" held from 12 to 14 May 2010 in Geneva and were subsequently modified[2] based on input received during a teleconference held on 10 June 2010.

[2] Texts in italic reflect main changes introduced during the teleconference's discussion and comments received on the revised draft.

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Annex 1

Informal consultation with the ad hoc committee on vaccines prequalification for the revision of the procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations Agencies

WHO Geneva, Switzerland

12-14 May 2010

White Paper

Revised approaches to testing final product characteristics

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1) Background

The testing of three to five final lots for checking consistency of final product characteristics is performed as part of the Prequalification process of novel and traditional vaccines. This activity is also performed to continuously monitor the quality of prequalified vaccines or vaccines that are being investigated due to complaints or AEFI reports received from the field. Lots are tested in parallel by two independent WHO contracted laboratories.

In order to face the increased demand and the complexity of control for evaluation of vaccines of all types and the need to have more WHO contracted laboratories to perform those testing activities, increased human, specific expertise and technical resources are required. Specifically, the extent of testing to be put in place has increased significantly as well as the need to standardize and validate new testing methodologies to verify final product characteristics of novel vaccines.

2) The Objective

The purpose of the consistency testing on final product characteristics is to verify that the vaccines meet the specifications of the relevant WHO recommendations as stated in the Technical Report Series and UN tender specifications. This is to ensure that vaccines used in national immunization services in different countries are consistently produced and controlled according to the WHO recommendations.

3) Problem statement/ challenges faced

Currently the PQ process is being challenged by:

- Increased demand for evaluation of vaccines of all types, complexity of the control methods and the need to have more WHO contracted laboratories to perform those testing activities

- Novel vaccines and new combinations to be evaluated (rotavirus, pneumococcal, HPV, possibly JE).
    - Need for new tests and increased complexity
    - Less expertise available and few laboratories performing those tests
    - Inconsistent results between laboratories
    - Need for standardization and harmonization of test methodologies

4) Current ad-hoc solutions in place

While the testing capacity for novel vaccines such as rotavirus, pneumococcal conjugate and HPV vaccines is being established in laboratories that are contracted by WHO for other tests new approaches to assess novel vaccines have been implemented because the testing capacity was not present at the time when these products were under evaluation. However testing capacity is needed to control the vaccines after prequalification is granted, as part of the random testing activities performed on samples of vaccines distributed by the UN procurement agencies.

The current system for assessing laboratories to be contracted by WHO includes review of the relevant testing documentation (validation report, trends, SOPs, Proficiency or collaborative studies report), testing in parallel with an already contracted laboratory and visit to the laboratory to assess facilities and the quality system in place when deemed necessary.

New approaches to assess laboratories already certified by internationally recognized organisms (eg EDQM, UKAS) have been taken. Parallel testing with already contracted laboratories and some documentation to show performance of the laboratory on the required testing (eg. trends, SOPs, validation reports) are assessed by WHO. However visit to the facilities may be waived if the laboratories have already been assessed by well known accreditation bodies.

5) Proposal

- To develop a procedure which will guarantee that the vaccine submitted for initial evaluation for PQ complies with the WHO TRS and UN tender specifications, so as to minimize resources and streamline the testing procedures.

- To establish additional criteria for the targeted testing program (also called random testing) and for vaccines tested as a result of complaints or reports of AEFIs received from the field.

Testing approach for initial evaluation of vaccines submitted for Prequalification.

Vaccines submitted as part of initial evaluation will be categorized by WHO into one out of four categories described in the table 1 which is self-explanatory.

WHO recognizes the lot release testing performed by the NCLs responsible for the regulatory oversight of the vaccines which apply stringent standards for quality similar to
those recommended by WHO (eg Technical Report Series and other internationally recognized documents).

Testing results from WHO contracted laboratories and /or from laboratories accredited by independent organizations (either national or international) will be reviewed and accepted if a decision to waive the testing activities during the initial evaluation for PQ is taken.

Based on the available information provided by the responsible NCLs for the lot release testing of the vaccine submitted for PQ (eg raw data, trends, control charts) WHO may consider if additional independent testing by WHO contracted laboratories is required.

Table 1: Testing approach for initial evaluation for PQ

Category	Criteria	WHO requirements/testing approach	Requirements from the manufacturer before prequalification is granted	Requirements post PQ
I	Novel vaccine or new combination released by a competent NRA/NCL responsible for the regulatory oversight. NCL is performing the critical tests on a regular basis	• Review of UN tender aspects through samples of the vaccine in the final packaging presentation (to be submitted with the PSF) • Review of the testing results by the manufacturer and the NCL (raw data) of minimum 3 lots formulated from consecutive bulk lots • Review of the trends of the testing results of the NCL (if applicable)	• Detailed SOP for testing the product characteristics (relevant tests) • Biological reagents and reference materials for the validation of the tests by WHO contracted laboratories • Transfer of the relevant method by the manufacturer to the relevant laboratories through WHO	• Commitment from the manufacturer to keep retention samples for testing by WHO contracted laboratories • Testing of the vaccine through the targeted testing program
II	Novel vaccine released by a competent NRA/NCL responsible for the regulatory oversight Validation of the critical tests is in progress.	• Review of UN tender aspects through samples of the vaccine in the final packaging presentation (to be submitted with the PSF) • Review of the testing results by the manufacturer (raw data) of minimum 3 lots formulated from consecutive bulk lots • Review of the trends of the testing results of the NCL (if applicable) • Agreement with the NCL to validate the tests during the PQ evaluation • Agreement to perform and provide results to WHO before PQ is granted	• Detailed SOP for testing the product characteristics (relevant tests) • Biological reagents and reference materials for the validation of the tests by WHO contracted laboratories • Transfer of the relevant method by the manufacturer to the relevant laboratories through WHO	

Table 1: Testing approach for initial evaluation for PQ

Category	Criteria	WHO requirements/testing approach	Requirements from the manufacturer before prequalification is granted	Requirements post_PQ
III	Traditional vaccine released by a competent NRA/NCL responsible for the regulatory oversight. NCL is performing the critical tests on a regular basis	• Review of UN tender aspects through samples of the vaccine in the final packaging presentation (to be submitted with the PSF) • Review of the testing results by the manufacturer and the NCL (raw data) of minimum 3 lots formulated from consecutive bulk lots • Review of the trends of the testing results of the NCL	• Detailed SOP for testing the product characteristics (relevant tests) • Biological reagents and reference materials for the tests by WHO contracted laboratories	• Commitment from the manufacturer to keep retention samples for testing by WHO contracted laboratories • Testing of the vaccine through the targeted testing program
IV	Novel or traditional vaccine NRA/NCL responsible for the regulatory oversight does not perform the critical tests	• Review of UN tender aspects through samples of the vaccine in the final packaging presentation (to be submitted with the PSF) • Testing by WHO contracted laboratories before the PQ is granted • Agreement with the NCL to validate the tests	• Detailed SOP for testing the product characteristics (relevant tests) • Biological reagents and reference materials for the validation of the tests by WHO contracted laboratories • Transfer of the relevant method (if applicable) by the manufacturer to the relevant laboratories through WHO	

Category 1

The applicant will inform the responsible NRA/NCL for the regulatory oversight of the vaccine of its submission to WHO for prequalification evaluation and shall grant authorization to the NCL to disclose the testing results (raw data) to WHO.

Testing of samples may be waived. However the manufacturer should send the relevant information as well as the biological reagents and reference materials indicated in the table and should transfer the test methodologies to the relevant laboratories through WHO.

In addition, the applicant will inform WHO if other NCLs have tested the vaccine for lot release purposes, data from these alternative authorities can also be made available upon request.

The targeted testing program will be performed as per standard procedure indicated below.

Category 2

The applicant will inform the responsible NCL of its submission to WHO for prequalification evaluation and shall grant authorization to the NCL to disclose the testing results (raw data) to WHO.

The NCL should agree to validate the tests and to send the results as soon as they are available. Previous receipt of the data is necessary for prequalification

Testing of samples may be waived. However the manufacturer should send the relevant information as well as the biological reagents and reference materials indicated in the table and should transfer the test methodologies to the relevant laboratories through WHO.

In addition, the applicant will inform WHO if other NCLs have tested the vaccine for lot release purposes, data from these alternative authorities can also be made available upon request.

The targeted testing program will be performed as per standard procedure indicated below.

Category 3

The applicant will inform the responsible NCL of its submission to WHO for prequalification evaluation and shall grant authorization to the NCL to disclose testing results (raw data) to WHO.

Testing of samples may be waived. However the manufacturer should send the relevant information as well as the biological reagents and reference materials indicated in the table upon request.

In addition, the applicant will inform WHO if other NCLs have tested the vaccine for lot release purposes, data from these alternative authorities can also be made available upon request.

The targeted testing program will be performed as per standard procedure indicated below.

Category 4

The applicant will inform the responsible NCL of its submission to WHO for prequalification evaluation.

Testing of samples by WHO contracted laboratories will be performed before the PQ is granted. The manufacturer should send the relevant information as well as the biological reagents and reference materials indicated in the table. .

In addition, the applicant will inform WHO if other NCLs have tested the vaccine for lot release purposes, data from these alternative authorities can also be made available upon request.

It is proposed that the list of WHO's contracted laboratories be posted on the PQ webpage in the future.

However to promote the independence and impartiality of the testing neither the manufacturer nor any other party who may have requested that vaccines be tested through this system will be informed where the testing is actually performed. On request, the manufacturer and the relevant NRA/NCL will, however, receive a report of the test results.

Monitoring of continued compliance with specifications through targeted testing program.

Samples of lots supplied through UN Agencies will be selected, at least once a year, for independent testing of final product characteristics. An appropriate number of samples (between 50 and 150 depending on the vaccine type and presentation offered) of three to five lots selected by WHO from a list of products supplied to UN agencies will be requested from the manufacturer. These will be sent by WHO to their contracted laboratories for testing. The manufacturer will provide lot summary protocols and the NRA/NCL release certificate as appropriate, will provide information on lot release for review. Manufacturers should commit to keep adequate number of retention samples for this testing program.
Manufacturers will, in any case be contacted for follow-up actions in case of failure to meet specifications.
In the event of failure to meet the established criteria WHO will investigate the problem and provide the UN agency with written information, copied to the manufacturer and the NRA, on the actions that need to be taken.

Monitoring of complaints or AEFI from the field: testing approach.

Adverse Events following immunization (AEFI):

The targeted testing program performed by WHO on a continuous basis supports the continued compliance of the vaccine with the established quality specifications. In addition testing results gathered during the lot release process by the NRA/NCL is requested from the NRA/NCL exercising the regulatory oversight of the vaccine when the AEFIs are investigated. Further testing will be resource-intensive and will not yield useful data.

- Therefore the testing of a vaccine lot/batch would only be recommended if the clinical and/or epidemiological information about the AEFI case(s) indicates a potential vaccine quality problem and after review of the relevant manufacturing and control documentation. The review of the batch records by the manufacturer and the NRA exercising the regulatory oversight of the vaccine allows for detection of any potential deviation during the manufacturing process that may impact on the quality of the vaccine..
- The outcome of the investigation of AEFI cases would indicate if testing is required and in such case which specific type of testing is needed.
- Depending on the tests to be performed, the number of un-opened containers (sampled from the field and from the manufacturer) required for testing needs to be statistically calculated, so that it is powered enough to draw definitive conclusions about the relevant lot. In the event that testing is needed, WHO would contact one of the WHO contracted laboratories that could perform the test and subsequently inform the national authorities of the number of vaccine vials to be sent as well as other logistic arrangements.

Vaccine quality complaints:

In case of vaccine quality complaints, WHO may perform independent testing after review of the relevant information including review of the temperature monitoring devices, review of the testing results and related data.

In case of complaints from NCLs different from the NCL exercising the regulatory oversight review of the testing results and related documentation such as validation reports, SOPs, control charts is needed for WHO review..

Handling of OOS/inconsistent results between laboratories.

Due to the increased complexity of the vaccines and new combinations currently available or in the pipeline for prequalification, the diversity of the methods applied for the quality control of the vaccines; the consistency/inconsistency of testing results obtained by WHO contracted laboratories may pose challenges for the evaluation of the results.

In the case of inconsistent results by two WHO contracted laboratories, WHO may require to send samples of the vaccine to a third laboratory.

WHO may convene an Ad Hoc Committee to assess the combined results. Representatives from the WHO laboratories may take part in this committee. Recommendation from the Ad Hoc Committee will be then considered as final by the WHO Secretariat.

Recommendations for action in cases of failure.

In the event of situations of failure to meet the established specifications detected during the initial evaluation and/or through the targeted testing program or complaints received from the field, and depending on the nature of the failure, WHO may recommend one or more of the following:

- The manufacturers' lots of vaccines be more closely monitored through additional testing, visit to the manufacturing facilities together with the NRA responsible for the regulatory oversight of the product and review by WHO of the corrective/preventive actions during a probationary period that will depend on the failure
- Purchase of the vaccine by UN agencies be suspended pending investigation and resolution of the problem

The failures related to some gaps in the manufacturing and/or quality system in place by the manufacturer may require a complete reassessment of the vaccine.
WHO will inform the relevant NRA responsible for the regulatory oversight about problems in the field or failure to meet established criteria.

6) References

Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. WHO/IVB/05.19. World Health Organization, 2006.
http://www.who.int/vaccines-documents/DocsPDF06/812.pdf*

Annex 2

Informal consultation with the ad hoc committee on vaccines prequalification for the revision of the procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations Agencies

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White Paper

Streamlining the prequalification procedure: Consideration of a risk-based approach

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The members of the working group have contributed *à titre personnel.* The content of this document does not necessarily reflect the position of the organizations represented by the working group members.

1) Background

The number of submissions, the diversity and complexity of the vaccines submitted to

WHO as part of the prequalification (PQ) procedure, as well as other activities related to this procedure are increasing. Vaccines may now include new antigens, more antigens in one presentation, new adjuvants, multiple manufacturing sites, etc., thus necessitating WHO either accessing a broader range of technical expertise and/or conducting what in effect are lengthier and more complex reviews. The on-going "maintenance" of what is an ever-growing portfolio of vaccines, that is, reassessments and reviews of variations, and investigation of potential quality concerns reflected in incident reports from the field, also translate into a growing workload for WHO. At the same time that the workload is increasing, the number of WHO staff dedicated to PQ activities is expected to remain the same or stable.

The regulatory landscape is also changing. The level and quality of the regulatory oversight at the local level has seen qualitative improvements in recent years and WHO's regulatory capacity building program has contributed to an improvement in the regulation of vaccines as more regulatory bodies are becoming functional in terms of WHO's six recommended regulatory functions.

Increased collaborations and mutual recognition have been established between regulators through mechanisms such as the PIC/S, whose membership has expanded beyond Europe to be more global in scope, the mutual recognition initiative in the ASEAN region, the International Conference for Harmonization (ICH) and other multilateral and bilateral initiatives underway among National Regulatory Authorities (NRAs). In general, these regulatory collaborations seek to enhance work-sharing and trust and are using risk-based approaches to deploy limited resources and evaluate risks in a more efficient manner.

The gap between resources and demand became recently acute during the H1N1 pandemic and an interim streamlined procedure was put into place as a pragmatic response to the immediate needs to prequalify H1N1 vaccines. A formalized revision to the current prequalification procedure needs to be undertaken, both in response to the increasing workload in the context of limited human resources, but to also take advantage of the changing regulatory environment and its potential contributions. A modified PQ procedure could allow the limited WHO resources available today to be reallocated to those parts of the procedure and to those vaccines with "relative" greater risk.

2) Objective

To provide the basis to develop in a short term a procedure, using a risk-based approach, in which WHO could place increased reliance on the regulatory review of a submitted vaccine, conducted by the responsible NRA (the NRA of the country of manufacture) deemed to be competent by WHO, resulting in reduction of review time for certain parts of the application and an optimal allocation of resources while ensuring the quality, safety and efficacy of vaccines submitted for prequalification.

3) Problem statement/ challenges faced

As mentioned in the *Background,* WHO is faced with an increasing workload in both quantity and complexity with respect to the PQ procedure, exceeding WHO's available capacity. This is a trend that it is likely to continue in 2010 and beyond. With limited human and financial resources, WHO cannot sustain the PQ procedure as it is currently configured and needs to consider alternative approaches.

4) Current ad-hoc solutions in place

The current official vaccine prequalification procedure is documented in the 2006 "Procedure for assessing the acceptability, in principle, of vaccines for purchase by UN agencies" (http://whqlibdoc.who.int/hq/2006/WHO_IVB_05.19_eng.pdf). This document details the steps of the procedure, defines the nature and the format of the information to be submitted by the applicants, known as the Product Summary File (PSF), and addresses confidentiality and conflict of interest issues.

The current procedure introduced some changes with respect to the previous version of the procedure in an attempt to increase the efficiency and capacity of response. For example, the establishment of three fixed submission deadlines per year. This, together with advance information from manufacturers about expected submissions has significantly improved the possibility of planning the work in advance. This also has made it possible for the review of technical aspects of the PSF to be done during a one-week working session in Geneva.

Although an attempt to address the changing trend in quality and quantity of submissions was made already in the current procedure, other needs were identified since 2006, which required certain adjustments to the procedure as detailed in this document. Changes have been made over time in an *ad hoc* way to adapt to pragmatic considerations that have arisen during the implementation of the procedure. For example, the procedure states that independent testing by WHO contracted laboratories is part of the initial evaluation process; however this requirement could not be fulfilled for some of the novel vaccines. The current *ad hoc* practice implemented for some of the novel vaccines is that results from tests performed by the responsible National Control Laboratory (NCL) were reviewed and accepted as surrogate of independent testing by WHO contracted laboratories. The reason for this change being that the required tests were implemented in limited number of laboratories, on occasions just in the NCL of the producing country.

To meet the ever expanding workload, WHO has had to increase its number of temporary staff based in Geneva as well as the number of temporary advisers engaged in the review of the documentation and execution of site visits. As noted already, this expansion cannot continue.

In order to respond to the H1N1 pandemic in a timely way, WHO also instituted an interim procedure using a risk-based, scientifically-based approach which streamlined the

overall prequalification process. The urgent need for prequalified pandemic influenza vaccines and the fact that the production processes and quality control of seasonal and pandemic influenza vaccines are similar but for the strain(s), led to an approach where it was possible for WHO to use the reviews of NRAs rather than undertake its own full review, based on the level of experience of the manufacturer and the NRA. This procedure is described in more detail in Annex 1.

5) Proposal

5.1 Example of first experience with risk-based approach: Pandemic influenza vaccines

As noted above, WHO has evaluated, and continues to evaluate, pandemic influenza vaccines using a risk-based interim procedure. To-date, nine pandemic vaccines, produced by three manufacturers already producing prequalified seasonal influenza vaccines, have been accepted with a review of programmatic aspects only (no review of the PSF). Two pandemic vaccines, manufactured by manufacturers that have experience with production of influenza vaccines but do not produce a prequalified influenza vaccine, have been reviewed using a fast track procedure which was executed within 20 working days.

In the fast track procedure, the assessment and inspection reports of the responsible NRAs were reviewed by WHO experts and not the PSF itself. Additionally, in each case, two-day site visits were carried out by WHO to discuss and review on-site questions that WHO deemed were not yet adequately addressed in the NRA reports and to evaluate compliance with WHO GMPs, focusing on safety, potency and consistency. All items were discussed with the responsible NRA as well. In both fast track cases, the assessing and site visiting teams recommended prequalification of the vaccines.

The experience showed the value of a complete NRA report for all aspects of the licensing file submitted by the applicant that included an overview of the manufacturing process and in-process controls and controls on intermediates and drug product.

5.2 Stratification of risks

A core principle used in the pandemic risk-based approach was the stratification of risk and this is recommended to be adopted as an underpinning to a streamlined option to the existing vaccine prequalification procedure. Stratification can be undertaken in a multi-factorial approach using both the overall level of experience of manufacturers and an enhanced assistance from responsible NRA's based on their functionality. Alternatively, a one-dimensional approach considering only the manufacturer experience, or the responsible NRA competence, could be adopted.

Risks involved in the use of vaccines that could be expected to be revealed by the review of the quality, safety and efficacy data can be stratified in the following way:

- Type of manufacturer (level of experience, number of vaccines already PQ-ed, outcome of recent site visits etc.)

- Type of regulatory oversight (executing full oversight, duration of existence of license, timely actions, etc.)

After considering both a "multi-factorial approach" (relying on both manufacturer experience and enhanced assistance from responsible NRA based on their functionality) and a "one dimensional approach" (relying on only one of these elements), it is recommended that WHO consider adopting an approach based on enhanced assistance from the responsible NRAs only, taking into account their agreement and capacity to contribute in accordance with the type of their regulatory oversight. It is felt that the multi-factorial approach is overly complicated and would be too big a challenge to implement.

5.3 Streamlined prequalification procedure based on enhanced assistance by NRAs

As was learned in the pandemic process, reliance upon effective regulatory oversight by the responsible NRA has the potential to play a critical role in the prequalification system. It is felt that this early experience in the pandemic flu context where WHO was able to take advantage of the responsible NRA's review can be extrapolated to other vaccines.

Assistance by responsible NRAs can lead to increased efficiency and resource saving by one or more of the following actions:

- Replacing WHO's evaluation of the PSF with a review of responsible NRA assessment reports
- Replacing WHO's testing of samples with a review of the batch release test results of National Control Laboratories NCL(s) and their trending of the results
- Replacing WHO's full site visit with a review of inspection reports from the responsible NRA and a short site visit by WHO.

However, reliance on the responsible NRA does have its limits. Since the responsible NRA would be focusing their review on data relevant to their own population, their approval would not be automatically applicable for the world-wide use of a vaccine in UN-type schedules and populations. In this respect the EMA Scientific Opinion procedure (Article-58) represents the exception. For all other authorities, the clinical data, in particular, would remain one of the aspects that need to be reviewed by WHO. For the clinical assessment it remains necessary to consider the clinical development program, the extent and validity of the conduct and outcome of individual clinical trials, and the provision for ongoing post-market pharmacovigilance and other risk-mitigation activities.

Typically, the responsible NRA would neither focus their review on aspects that are specific to the UN population immunization schedules and programme needs which are reflected in the UN tender specifications. These would need to be assessed by WHO.

In view of the above, a review by WHO of the aspects listed below would remain essential:

a) Confirmation that the vaccine meets WHO recommendations
b) Review of clinical data to ensure that is applicable to the target population
c) Review of stability data to ensure it meets the needs of immunization programs in developing countries (particularly those with weak cold chain systems) and to assign a VVM category
d) Review of recommended immunization schedules to ensure compatibility with those existing in national immunization programs and non interference with co-administered vaccines
e) Review of the suitability of samples, labels, inserts and packaging to meet the UN Agency tender requirements
f) Review of mandatory, critical and preferred product characteristics from the programmatic point of view, which should be addressed during the screening of the submitted PSF for completeness
g) Review of packaging for international shipment and its validation
h) Recommendation that the vaccine would be eligible for the Advanced Market Commitment (AMC) through review of target product profile
i) For vaccines that are licensed exclusively for export purposes, an expanded review by WHO may be required

In addition to establishing the criteria for selection of NRAs that are eligible in principle, it is necessary that WHO would need to explicitly request the assistance of the responsible NRA when WHO opted to rely heavily on their assessment of the product. Moreover, a consultation meeting with the responsible NRA would be crucial in those situations. Such a consultation would provide the opportunity to address critical issues not fully covered by the responsible NRA's reports. It is anticipated that such interactions would require the establishment of a formal mechanism between WHO and the responsible NRA that would outline the shared understanding of roles and responsibilities in the collaboration.

Therefore, the implementation of the proposed streamlined approach requires an eligible authority and the willingness of this authority to enter in this collaborative effort. Special consideration should be given to authorities from countries where English is not the mother tongue. In such cases, engagement in this exercise would imply additional workload for the NRA to make their reports available in English. Specificities of the collaboration (nature and extent) should be defined on a case by case basis and reflected in the agreement.

5.4 Proposal for accepting NRA reviews / oversight

It is proposed that in addition to the standard WHO vaccine prequalification procedure, a streamlined option be established which envisions the reliance, on the oversight performed by a responsible NRA, using a risk-based approach. If a responsible NRA exhibits a high level of performance of WHO's six recommended regulatory functions and exercises its regulatory responsibilities in the full oversight of any given vaccine, the experience level of the manufacturer becomes a non-issue from the WHO's perspective. Therefore, it is recommended that risk factors underlying the streamlined option be limited to a stratification of responsible NRAs.

The process and factors to consider in such a screening approach would need to be developed as a separate undertaking by WHO which could take some time to achieve. Therefore this Working Group proposes an intermediate modus operandi to provide with little effort a streamlining that can be achieved in a short period of time using the current process of determining the functionality of NRAs. That is, streamlining of the prequalification procedure may be applied to vaccines evaluated by those NRAs that have been assessed as functional by WHO and who are willing to share with WHO information concerning their approval and oversight of the vaccine. Because a "functional" determination by WHO may still reflect weaknesses or gaps in the NRA's oversight per the WHO six criteria, an additional evaluation step of interested NRAs can be performed in the following way:

1) *Preliminary condition for a product to benefit from a streamlined PQ procedure:* WHO will (in any case) establish completeness of any submitted PSF by screening of the PSF. A PSF showing serious gaps in critical information submitted for a candidate vaccine, and registration granted in spite of the absence of such "critical" data would reveal a lack of strength in the regulatory oversight of the product and would automatically move this product (if passing the screening at some point in time) to the full evaluation category.

2) *Eligibility of the NRA for further collaboration:* The reviews of three vaccines made by the responsible NRA and those made by WHO on the basis of the submitted PSF are compared (subject to authorization by the manufacturers and NRA concerned) to establish the level of similarity in the decision-making to license/pre-qualify the vaccine. The review of the NRA and WHO reports can be done retrospectively based on already approved and prequalified vaccines and / or concurrently based on newly submitted vaccines.

3) *Collaboration with the NRA:* In case similarity has been demonstrated for the three vaccines. the PQ team and the eligible NRA establish a collaboration agreement with WHO. The scope of this agreement can be determined by both parties and could include any or all of the following (each subject to authorization by the manufacturer):

- Sharing of NRA assessment reports of technical, non-clinical and clinical evaluation
- Sharing of NRA test results (including the raw data)
- Sharing of inspection reports

4) *The streamlined PQ procedure:* if the above (item 3) applies, WHO may decide to do any or all of the following:

    - review NRA assessment and inspection reports (instead off review of PSF) plus follow-up on queries and review of all items defined under item 5.3. The applicant will provide PSF or PSF with references to an enclosed Common Technical Document (CTD) file for the relevant items
    - waive testing of samples (provided NRA has tested a minimum of three consistency lots for critical parameters such as potency, antigen content or other as relevant and has routine testing in place as part of lot release as a minimum on a proportion of lots released; this will not affect random testing after PQ granting)
    - launch a short site visit consisting of two days emphasizing on outstanding questions, a tour of facilities and assessment of UN tender related matters; no GMP evaluation will be performed

The reviews made by the responsible NRA and made by WHO are similar, unless:

1. a change in production, QC or QA was needed for PQ and this was not included in the licensing file or
2. an additional clinical trial was needed for PQ and this was not included in the licensing file or the target population considered by WHO is different from the 'licensed' population or
3. an additional validation or qualification was needed for PQ and this was not included in the licensing file

Additional quality-related studies needed (e.g. stability) for PQ not included in the licensing file specifically needed to meet UN specifications will not be taken into account in establishing similarity or dissimilarity of NRA and WHO reviews.

Similarity can be demonstrated for all three review items (assessment reports, inspection reports and sample testing) or for any subset of these items. Enhanced reliance on the NRA can be applied accordingly.

Some of the vaccines offered for PQ are complex, with more than one NRA concerned in the control of active ingredient manufacture, formulation, filling and packaging (see also chapter 7 of the current procedure, “Special considerations for vaccines formulated and filled by different manufacturers in the same or different countries”). This will be addressed by another working group.

PQ Assessment of vaccines produced for export-only requires special consideration and possibly extended review by WHO as stated under h) in item 5.3, and case by case agreements with the relevant NRA may be needed.

Some NRAs do not require renewing the license on a regular basis. In such cases the NRA should have an alternative mechanism to monitor the continuing quality, safety and efficacy of the vaccines over which they exercise the regulatory oversight. Updated information on these vaccines should be conveyed to WHO by the NRA at defined intervals. This information might feed the reassessment procedure .

5.5 From theory to practice

The submission for prequalification would still require providing a PSF format or an abbreviated PSF providing the information that is part of a PSF but not of a CTD together with a dossier with CTD format with a table of cross references to the CTD chapters for the rest of the information. Several reviewers have expressed a strong preference for the PSF format.

The streamlined approach can be implemented by starting a pilot test with a limited number of NRAs and relevant applications during the first year of implementation. Once the procedure is settled, a step-wise expansion can be carried out in one or two years.

Once an assessment procedure of NRAs distinguishing more levels of functionality becomes available and operational a more sophisticated risk-based approach can be applied.

One disadvantage of the streamlined approach could be that the WHO (-associated) staff/experts gradually become less exposed to the wide range of products and manufacturers and the associated information. This level of exposure is essential in maintaining expertise; an effort shall be made to at least maintain expertise.

It is hard to predict whether the streamlining and enhanced support by NRAs as proposed in this document will be sufficient in view of the increasing numbers of applications from countries with less robust NRAs.

In a world where science and authorities are exposed to increasing criticism and even scepticism a change in WHO policy needs to be accompanied by transparency and clear messages to the stakeholders and media.

As bad news sells better than good news an effort should be made to clarify that WHO is not doing less but rather that limited resources are allocated in a more efficient manner, resulting in an even further increase of demonstrated quality, safety and efficacy of vaccines that already have served the world to a great extent.

Annex 1

Procedure and experience prequalifying pandemic influenza vaccines

The procedure (http://www.who.int/immunization_standards/vaccine_quality/expedited_proc_pandemic_flu_final290909.pdf) distinguished four categories (see table below).

Category	Criteria	WHO assessment approach	Time for process at WHO
I	Seasonal influenza vaccine is prequalified by WHO Pandemic influenza A (H1N1) 2009 vaccine is licensed by NRA of record	Review of programmatic aspects	1 working day from the time of reception of the documentation
II	Seasonal influenza vaccine has not been prequalified by WHO Seasonal and pandemic influenza A (H1N1) 2009 vaccine licensed by NRA of record Other vaccines from same company are prequalified	Review of NRA assessment reports Review of NRA test results, or independent testing of samples Site visit may be waived on the basis of availability of GMP inspection reports Review of programmatic aspects	10 working days (if site visit is waived) 20 working days (if site visit is needed) from the time of reception of the documentation
III a)	Seasonal influenza vaccine has not been prequalified by WHO, but manufacturer has experience in the production of flu vaccines Seasonal and pandemic influenza A (H1N1) 2009 vaccine licensed by NRA of record No other vaccine from same company is prequalified NRA meets WHO criteria	Full assessment process to be conducted on fast track basis, in consultation with NRA and based on a site visit	Full assessment process to be conducted on fast track basis, 20 working days from the time of reception of the documentation

III b)	Seasonal influenza vaccine has not been prequalified by WHO and manufacturer has no prior experience in the production of flu vaccines Pandemic influenza A (H1N1) 2009 vaccine licensed by NRA of record No other vaccine from same company is prequalified NRA meets WHO criteria	Full assessment process to be conducted on fast track basis.	6 months from the time of reception of the documentation (excluding time taken by manufacturer to respond to queries)
IV	NRA does not meet WHO criteria	Not acceptable for prequalification evaluation	

Already nine pandemic vaccines (produced by three manufacturers) have been accepted as category I vaccines with a review of programmatic aspects only (no review of PSF). Two vaccines have been reviewed and prequalified as category II vaccines so far. In short the following has been carried out (examples have been made anonymous):

Number 1, the vaccine was fully reviewed by the NRA in charge. The NRA provided all relevant assessment and inspection reports (total of 11 documents) which have been reviewed by assessors. A 7-pages' report with 24 questions has been forwarded to the applicant.

After receiving the response of the applicant the outstanding issues were:

1 Proof of consistency of production
2 Validation of potency test, trending of reference preparation, comparing with results of NCL in charge and 2nd NCL.
3 Validation of sterility test (with thiomersal containing samples)
4 Preservative efficacy, part of stability testing (was not completed)
5 Justification for use in the xx-yy years age group.

A two days' site visit was carried out to discuss and review at the site questions that were not yet adequately addressed and to evaluate compliance with WHO GMP by emphasizing on safety (inactivation, test on inactivation, sterile filling; including validations), potency (potency test, including validation) and consistency (release data).

All items were also discussed with the NRA in charge.

Number 2, the vaccine was reviewed by the NRA in charge as a strain change. The NRA provided all relevant assessment and inspection reports (total of 5 documents) which have been reviewed by assessors. As the NRA had reviewed the submission as a strain change the provided assessment reports revealed limited information; the inspection reports were full reports.

Therefore it was decided to review also part of the PSF (production and QC) and a total of 17 questions such as related to QC – QA relationship, possible use of new master seed lot, safety tests (and change in the specifications of one of these tests), potency test, quality of biological source materials, consistency and distribution have been raised. There was no time for a response before the site visit.

A two days' site visit was carried out to discuss all questions raised and to evaluate compliance with WHO GMP by emphasizing on safety and potency tests and their validations and consistency (release data).

All items were also discussed with the NRA in charge. After the site visit the applicant sent the responses as discussed.