

Assessing the programmatic suitability of vaccine candidates for WHO prequalification

(Revision 2014)



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Contents

1.	Foreword.....	1
2.	Background	3
3.	Purpose of this document	4
4.	Vaccine characteristics that determine programmatic suitability	5
4.1	<i>Sources of information</i>	5
4.2	<i>Types of vaccine characteristics</i>	5
4.3	<i>Vaccine characteristics that will affect the acceptance for prequalification</i>	7
4.3.1	Mandatory characteristics.....	7
4.3.2	Critical characteristics.....	8
4.3.3	Unique or innovative characteristics	11
4.4	<i>Preferred characteristics: vaccine characteristics that reflect programmatic preference but will not affect the acceptance for prequalification evaluation</i>	11
4.4.1	Vaccines still in development	14
5.	The process of screening vaccine candidates before evaluation of the Product Summary File (PSF)	15
5.1	<i>The PSPQ Standing Committee</i>	17
6.	Procedure for consultations requested by vaccine manufacturers before submission of an application for WHO prequalification	18
7.	Implementation of the PSPQ requirements.....	19
7.1	<i>Timeline for implementation of the revised PSPQ</i>	19
7.2	<i>Procedure for changes to PSPQ process and criteria</i>	20
8.	Summary and conclusions	21
9.	References	22
10.	Appendices	23

1. Foreword

The aspiration of an ideal vaccine - one that is low cost, high efficacy, heat stable, freeze tolerant, multi-antigen, user friendly and environmentally friendly - is currently a hopeful dream. Yet, it is critical to uphold its attainment as the driving force for the development of new and innovative vaccines.

In recent years, the drive towards accelerated new vaccine introduction in developing countries has tended to emphasize the important social benefits of reduced morbidity and mortality, in some cases accepting product presentations lacking many of the highly desirable product characteristics mentioned above.

As a result, new vaccines have emerged that, although generally safe and effective in the prevention of major diseases, often incorporate characteristics that are undesirable in a developing country setting — complex handling, high cold-chain capacity requirements, complex waste-disposal requirements and very high cost.

Experience has shown that, once a new vaccine product reaches the clinical trial stage, it is extremely costly and time-consuming to reformulate the product in order to incorporate additional characteristics that were not contemplated in the original experimental design. It is therefore crucial to consider packaging and presentation characteristics from the earliest stages of pre-clinical development both in developed and developing countries for vaccines of global usage. This is often done through reference to target product profiles.

It is important to disseminate guidance for industry, to assist product development teams and pre-clinical scientists, to identify characteristics and innovations that are highly valued in terms of future vaccine products intended for use in developing countries, and to vigorously encourage them to include those characteristics from the earliest stages of pre-clinical study. Previous work to develop such guidance includes that of the Malaria Vaccine Initiative¹, the Target Product Profile (TPP) for the Advance Market Commitment (AMC) for pneumococcal conjugate vaccines² and the Vaccine Presentation and Packaging Advisory Group, which more recently developed a Generic Preferred Product Profile (gPPP)³ for new vaccines. The World Health Organization (WHO) prequalification (PQ) process is the mechanism available to the international community to assess whether new vaccine products adequately feature mandatory, critical and preferred characteristics, and are suitable for use in developing countries. A manufacturer may contact the PQ Secretariat to discuss the compliance with mandatory, critical or any innovative characteristics during pre-clinical or clinical development stage, although no final, binding decision can be made until the dossier is submitted for prequalification.

To achieve standardization and uniformity of the programmatic suitability requirement for prequalification, vaccines that are already prequalified, or were in the process of prequalification at the time of the implementation of this process and which are not compliant with its requirements will follow a transition process, which is described later in the document.

A time-limited Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) Working Group was formed and charged with drafting an initial version of this document early in 2010. The PSPQ Working Group was made up of representatives from national ministries of health, international organizations (WHO, UNICEF, PAHO), vaccine industry and others with experience in the procurement of vaccines and the management of national immunization programmes.

2. Background

As part of WHO's vaccine prequalification (PQ) process, product summary files (PSFs) are assessed by the WHO PQ Secretariat to determine '*the suitability of the vaccine for the immunization services where it is intended to be used*' (p.6, WHO/IVB/05.19⁴). Assessed characteristics include '*... presentations offered ... labelling, information provided on package inserts ... , and packaging ...*'. This is part of the broader process intended '*to ensure that vaccines used in national immunization services in different countries ... meet particular operational specifications for packaging and presentation*' (p.1, WHO/IVB/05.19⁴). Also, WHO published a new *Technical Report Series (TRS) 978 Annex 6 "Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies"*⁵ in Feb 2013, replacing the earlier document (WHO/BS/2155.10).

The PQ process is focussed on the use of vaccines as outlined by the vaccine manufacturer. Any use of vaccine not outlined by the manufacturer is not taken into consideration in the PQ process, even though WHO may recommend "off-label" use of vaccines in certain circumstances.

Although the assessment of the suitability of vaccines for the immunization services where they are intended to be used has always been part of PQ, historically, the assessment of the PSFs to determine programmatic suitability had not been formally structured, with the outcome based on individual expert inputs and WHO PQ Secretariat consensus.

In recent years, the emergence of novel or unique vaccine presentations, such as relatively large packed volume pre-filled syringes that do not include an auto-disable feature, injection device materials that require non-standard disposal methods and fully liquid low multi-dose vials without preservative, has driven the need to explicitly define the characteristics that determine programmatic suitability and the process for assessing compliance with these characteristics.

3. Purpose of this document

In this document we wish to clearly describe the screening process and set of rules by which all prospective vaccine prequalifications will be judged in terms of their programmatic suitability for developing country public-sector immunization programmes. We also describe the consequences of not complying with these characteristics on the screening and PQ processes. Furthermore, we wish to indicate very clear preferences for future vaccines that will result in greater compliance with developing country needs, and that will facilitate universal immunization without requiring massive and unrealistic investment in additional cold-chain capacity, human resources, waste-disposal facilities, etc.

Hence, the purposes of this document are as follows:

- to define the characteristics that determine programmatic suitability;
- to define the process for assessing compliance with these characteristics;
- to indicate vaccine characteristic preferences to industry and other vaccine-development groups.

The characteristics described here are to be used in a screening process that is intended to avoid the resource- and time-consuming process of formal PSF evaluation for vaccine candidates that are not in compliance with programmatic suitability characteristics.

WHO prequalification of vaccines is a global process. Any additional characteristics may be required by regional or national procurement agencies in some instances regional variance in programmatic suitability characteristics will be expressed in the regional and national procurement and tendering process.

4. Vaccine characteristics that determine programmatic suitability

4.1 Sources of information

Vaccine characteristics that determine programmatic suitability were identified by reviewing existing WHO Department of Immunization, Vaccines and Biologicals (IVB) policy and technical guidance, by reviewing current discussions in WHO IVB advisory groups, such as the WHO Technologies and Logistics Advisory Committee (TLAC) in 2008/2009 and the subsequent WHO Immunization Practices Advisory Committee (IPAC), by reviewing the work of groups such as the Vaccine Presentation and Packaging Advisory Group (VPPAG), through discussion with immunization programme personnel and by reviewing other relevant documents.

During this process it was recognized that, over the past few years, several groups have developed advice and recommendations on issues related to the programmatic suitability of vaccines destined for use in the public sector immunization programmes of developing countries. These include target product profiles for pneumococcal, rotavirus and human papillomavirus vaccines, the gPPP developed by the VPPAG, and topic-specific recommendations from the Immunization Practices Advisory Committee (IPAC), such as those for thermostability.

4.2 Types of vaccine characteristics

Vaccine characteristics identified as determinants of programmatic suitability for prequalification are organized into three groups: mandatory, critical, and unique and innovative characteristics. A category of preferred characteristics is also identified (see Table 1 on page 6).

- ‘Mandatory’ characteristics: those for which compliance is compulsory at the time of application for WHO prequalification and which must be unconditionally met prior to evaluation of the PSF.
- ‘Critical’ characteristics: compliance with critical characteristics is also compulsory. However if, upon screening of the PSF, the PQ Secretariat identifies a deviation from the required value, it will refer the relevant section of the PSF to the PSPQ Standing Committee (PSPQ SC) and inform the manufacturer of the screening results (see Figure 2 on page 19). The PSPQ SC can then make a recommendation, consulting with the manufacturer and additional technical experts when needed, and taking into account the public-health need, to accept or reject the application for prequalification and the evaluation of the PSF.

- By definition, there is no guidance regarding vaccine candidates with characteristics or characteristic values not otherwise specified as ‘mandatory’ or ‘critical’. Because of this, vaccine candidates with unique and innovative characteristics will be referred to the PSPQ SC for review, discussion and recommendation.
- ‘Preferred’ characteristics are intended to reflect what WHO, procuring agencies and national immunization programmes would like to see as characteristics in vaccines intended for use in low and middle income countries. It is expected that national immunization programmes and procuring agencies will select vaccines with preferred characteristics over those that do not have these characteristics, all other being equal. Compliance with preferred characteristics is not compulsory although these characteristics may become ‘critical’ characteristics in the future. For vaccines still under development, these characteristics should serve as guidance to manufacturers on the minimum desirable standards.

The decision to grant approval to continue with the evaluation for prequalification can be taken only by the PQ Secretariat and Director EMP and will include consideration of recommendations from the PSPQ Standing Committee, issues such as the safety risk posed and the public-health importance of the vaccine, i.e., the impact on global and regional public health of a lack of access to the vaccine.

Table 1: PQ Secretariat decisions regarding compliance and deviations with vaccine programmatic suitability characteristics

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

4.3 Vaccine characteristics that will affect the acceptance for prequalification

4.3.1 Mandatory characteristics

Mandatory characteristics are those for which compliance is compulsory at the time of application for WHO prequalification and which must be unconditionally met prior to evaluation of the PSF (see Table 2 below and Figure 2 on page 16).

Table 2: Mandatory vaccine characteristics and characteristic values

Characteristic	Applies to...	Value
Anti-microbial preservative	Only injectable vaccines that: <ul style="list-style-type: none">are in ready to use (no reconstitution) presentation; andare in multi-dose containers of more than two doses per vial*.	The vaccine presented for prequalification should be adequately preserved (WHO/EPI). This is defined by having either the thiomersal concentration of >25 µg per dose (0.5ml) for monovalent hepatitis B vaccine and >50 µg per dose (0.5ml) for other vaccines) or the preservative having demonstrated its anti-microbial efficacy. The preservative efficacy should be tested using the methodology described in the European Pharmacopoeia (Ph Eur) [a challenge test over 28 days with specified microbes] and should demonstrate compliance with the "B" criteria of acceptance, or if justified, the criteria stated in the Ph. Eur monograph "Vaccines for Human Use" ⁶ .
Thermostability / storage	All vaccines	The vaccine or any component presented for prequalification should not require storage at less than -20°C (WHO EPI).
Dose volume	Only vaccines that are: injectable; and indicated for infants and/or young children (<5 years old).	The vaccine presented for prequalification should not be more than 1 ml per dose for indicated use in children aged 5 years or younger (WHO EPI).
Route of administration	All vaccines	The vaccine presented for prequalification should not require an intravenous route of administration.

* For countries receiving vaccine through UNICEF Supply Division or other UN Procurement agencies, the required procedure for ascertaining readiness of countries using pre-qualified inadequately preserved vaccine (see definition on page 9) in two dose vials should be maintained as follows:

- The country formally confirms in writing to the procuring agency the programmatic readiness upon conclusion of enhanced training with a special focus on conditions for storage of the 2 dose and placement of stickers on refrigerators at all levels indicating the need to discard this vaccine at the end of the vaccination session or after 6 hours
- A readiness assessment is undertaken in country by WHO and UNICEF country offices
- Upon WHO's communication to the procuring agency of the successful outcome of the assessment, UNICEF will notify the supplier that the first shipment can take place. The PQ team shall in the notice of pre-qualification of each individual vaccine make the appropriate statements of requirement in the pre-qualification approval.

However, the PQ Secretariat should in the notice of pre-qualification of each individual vaccine make the appropriate statements of requirement in the pre-qualification approval.

4.3.2 Critical characteristics

Compliance with ‘critical’ characteristics is also compulsory. However, if upon screening of the PSF the PQ Secretariat identifies a deviation from the characteristic value, then the PQ Secretariat will refer the application to the PSPQ SC and inform the manufacturer of the screening results (see Table 3 below and Figure 2 on page 16). The PSPQ SC can then make a recommendation, consulting with the manufacturer, vaccine procuring agents such as UNICEF SD and additional technical experts when considered necessary, to accept or reject the application and the evaluation of the PSF. Table 3 shows critical characteristics and their values.

Table 3: Critical vaccine characteristics and characteristic values

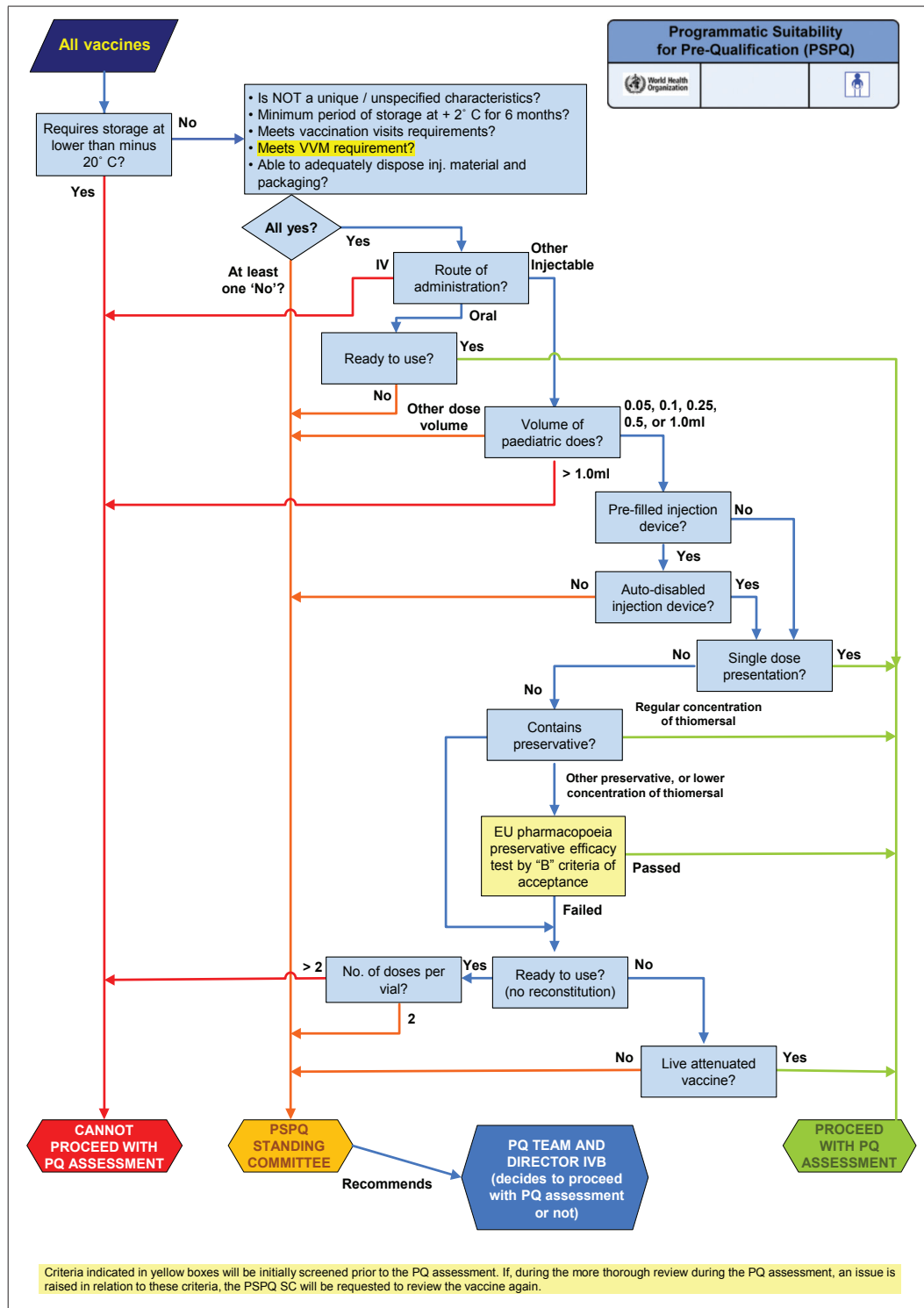
Characteristic	Applies to ...	Value
Vaccination visits	All vaccines	<p>The vaccine presented for prequalification should fit into currently commonly used schedules of vaccination visits. The following are deemed to meet this characteristic and do not require further review by the PSPQ Standing Committee:</p> <ul style="list-style-type: none"> • If the proposed vaccine is meant for use in children under five, and is recommended⁷ to be given at one or more of the following regular immunization visits: <ul style="list-style-type: none"> – within 24 hours after birth; and/or – at not more than three visits, 4 to 8 weeks apart, with the first visit at or after 6 weeks of age and the third visit at or before 6 months of age; and/or – at not more than two visits between 9 and 12 months of age; and/or – at not more than two visit between 12 and 24 months of age; and/or – at not more than one visit in the fifth year of life. • If the proposed vaccine is designed to be given to adolescents aged 9 to 15 years, and requires no more than four contacts through health service or school-based immunization programmes. • If the proposed vaccine is designed exclusively for use in reactive campaigns (pandemics, disasters, humanitarian emergency action) • If the proposed vaccine is given post-exposure. • If the proposed vaccine is targeted at individuals over 5 years of age, and dose intervals are two weeks or more apart. <p>If the vaccine does not fit into one of the above criteria, it must be reviewed by the PSPQ SC (WHO EPI)</p>
Process of preparation for administration	Oral vaccines	The vaccine presented for prequalification should be packaged in a ready-to-use format, i.e., does not have to be reconstituted (WHO EPI).
Thermo-stability / storage	All vaccines	If the vaccine presented for prequalification requires storage below +2°C during its shelf-life period, it should have a minimum period of storage above +2°C of 6 months (WHO/IVB/06.10 ⁸).

Characteristic	Applies to ...	Value
Vaccine vial monitor (VVM)	All vaccines	<p>Proof of feasibility and intent to apply a VVM to the proposed vaccine, as defined below.</p> <p>The vaccine presented for prequalification presents data confirming that it has a thermostability profile that will enable it to be matched to a current WHO-approved VVM type (VVM2, VVM7, VVM14 or VVM30) or a future VVM type that may be approved by WHO (WHO/IVB/07.04⁹).</p> <p>Signed declaration, as part of the cover letter submitted along with the file for prequalification confirming that the manufacturer will apply a VVM to the vaccine and has the technical capacity to do so if requested by the purchasing specifications.</p>
Materials, primary and secondary packaging, and injection material	All vaccines	The vaccine presented for prequalification should be packaged in materials that can be disposed of appropriately in the field using standard procedures (e.g., pit burning and burying, low temperature incinerations, etc.) (WHO EPI).
Pre-filled injection devices	Only vaccines that are delivered in pre-filled injection devices	The vaccine presented for prequalification in a pre-filled injection device should include an auto-disable (AD) feature (WHO/V&B/99.25) ¹⁰ .
Dose volume	Only injectable vaccines	The vaccine presented for prequalification should be dosed in standardized volumes (e.g., 1, 0.5, 0.25, 0.1, 0.05 ml) that can be easily measured using available AD syringes (WHO EPI).
Anti-microbial preservative	<p>Only vaccines that:</p> <ul style="list-style-type: none"> are in ready to use (no reconstitution) 2-dose vial presentations; <p>or</p> <ul style="list-style-type: none"> are not live attenuated, in multi-dose presentations and require reconstitution. 	<p>The vaccine presented for prequalification should be adequately preserved (WHO/EPI).</p> <p>This is defined by having either the thiomersal concentration of >25 µg per dose (0.5ml) for monovalent hepatitis B vaccine and >50 µg per dose (0.5ml) for other vaccines) or the preservative having demonstrated its anti-microbial efficacy. The preservative efficacy should be tested using the methodology described in the European Pharmacopoeia (Ph Eur) [a challenge test over 28 days with specified microbes] and should demonstrate compliance with the "B" criteria of acceptance, or if justified, the criteria stated in the Ph. Eur monograph "Vaccines for Human Use".⁶</p>

Please note: For the application of the Multi-Dose Vial Policy¹¹ (MDVP), a decision will be made if a multi-dose vial can be safely kept open for subsequent vaccination sessions, or if the vial should be discarded at the end of the session. For this decision to be made, vaccine manufacturers are required to include in the PSF submitted for PQ data on the antigenic stability of the vaccine for 28 days after reconstitution. These data will not be used to determine if the vaccine should or should not be pre-qualified, but (together with data on preservative efficacy) will enable the appropriate classification of the vaccine in respect of the MDVP. This decision will be made by the PQ Secretariat, based on the review of the data available to the PQ team. Should the vaccine have been referred to the PSPQ Standing Committee, the Standing Committee may make a recommendation on this decision, and the antigenic stability will then be taken into consideration.

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

Figure 1: Vaccine characteristics that affect acceptance for prequalification



4.3.3 *Unique or innovative characteristics*

By definition, there is no guidance regarding vaccine candidates with characteristics or characteristic values not otherwise specified as ‘mandatory’ or ‘critical’. As an example, unusual routes of administration (such as aerosol vaccination) would be considered a unique characteristic, and would be referred to the PSPQ SC for review.

Because of this, vaccine candidates with unique and innovative programmatic suitability characteristics will be referred to the PSPQ SC for review, discussion and recommendation. In such cases, manufacturers are advised to contact WHO at the early stages of vaccine development in order to discuss such characteristics, rather than first presenting them at the time of PQ evaluation.

Figure 1 on page 10 presents a flow chart that describes the vaccines’ characteristics and their effects on acceptance for prequalification.

4.4 **Preferred characteristics: vaccine characteristics that reflect programmatic preference but will not affect the acceptance for prequalification evaluation**

Preferred characteristics will not be reviewed or assessed by the PSPQ SC because these characteristics will not directly influence the prequalification process. However, it is expected that national immunization programmes and procuring agencies will select vaccines with these preferred characteristics over those vaccines that do not meet these characteristics, all other being equal.

Preferred characteristics are intended to reflect what WHO, procuring agencies and national immunization programmes would want in a best-case scenario and would expect in the future; these characteristics are intended as guidance to manufacturers. Compliance with preferred characteristics is not compulsory, although with time these characteristics may become ‘critical’ characteristics. Table 4 shows preferred characteristics and their values. Two preferred characteristics are scheduled to move to become ‘critical’ characteristics during the next PSPQ revision in two to three years. These criteria (labelling and barcoding) are indicated in the table below. It should be noted that this does not exclude other critical or mandatory characteristics being included or modified in the next revision of PSPQ.

Table 4: Preferred vaccine characteristics and characteristic values

Characteristic	Applies to...	Value
Antigenic stability after reconstitution	Only vaccines that: <ul style="list-style-type: none"> are in multidose presentations; and <ul style="list-style-type: none"> require reconstitution of one or more components; and <ul style="list-style-type: none"> are adequately preserved. 	<ul style="list-style-type: none"> Vaccines that show antigenic stability for 28 days after reconstitution are preferred.
Antimicrobial preservative	Only vaccines that are: <ul style="list-style-type: none"> In ready-to-use formulation (no reconstitution) and <ul style="list-style-type: none"> Inadequately preserved vaccine (see definition on page 9) 	<ul style="list-style-type: none"> Vaccines that are inadequately preserved (see definition on page 9) and in ready-to-use formulations (no reconstitution required) would be preferred in single dose presentations.
Maximum packed volume	All vaccines	<ul style="list-style-type: none"> A smaller packed volume is preferred. Where appropriate, components should be packed/ shipped together, e.g., for ready-to-use presentations: pre-filled AD syringe with needle, etc. Packaging devices should be considered to assure components are shipped together, e.g., vial clip. (WHO EPI, VPPAG gPPP: maximum packed volume; see <i>Guidelines on the international packaging and shipping of vaccines</i>¹²).
Dose volume	Oral vaccines	<ul style="list-style-type: none"> Smaller volumes and standardized volumes are preferred (WHO EPI).
Doses per primary container, non-campaign setting	All vaccines	<ul style="list-style-type: none"> Vials with ≤10 doses per vial are preferred (WHO EPI, VPPAG gPPP: optimal number of doses per primary container, work programme). Minimize number of doses per vial that cannot be reused in subsequent sessions once the container is open.
Doses per primary container, campaign setting	All vaccines	<ul style="list-style-type: none"> Vials with ≥ 10 doses per vial are preferred (WHO EPI).
Doses per secondary container	All vaccines	<ul style="list-style-type: none"> Should reflect logistics schedule and needs in order to minimize stock accumulation at the peripheral level (WHO EPI).
Process of preparation for administration	All vaccines	<ul style="list-style-type: none"> Single component/ready to use (e.g., liquid) formats are preferred (WHO EPI). For multi-component vaccines, provide vaccines in formats to minimise (1) number of steps, and (2) potential for error during preparation and administration (VPPAG-gPPP).
Container type	All vaccines	<ul style="list-style-type: none"> Except for separately packed diluents, vial-filled presentations are preferred over ampoule-filled presentations (VPPAG-gPPP)
Thermo stability / storage	All vaccines	<ul style="list-style-type: none"> Vaccines and diluents that can be stored for extended periods at temperatures above +8°C are preferred (IPAC). Vaccines with data and licencing allowing for higher temperature storage. If feasible, use 40°C as the current target threshold temperature. (VPPAG)

Characteristic	Applies to...	Value
Freeze sensitivity	All vaccines	<ul style="list-style-type: none"> Vaccines that are not damaged by freezing temperatures (<0°C) are preferred (IPAC)
Materials, primary and secondary packaging and injection material	All vaccines	<ul style="list-style-type: none"> Materials for delivery devices, primary containers and secondary and tertiary packaging that minimize environmental impact of waste disposal are preferred (VPPAG-gPPP).
Secondary packaging, diluents and vaccines	Vaccines requiring reconstitution	<ul style="list-style-type: none"> Diluents and vaccines should have the corresponding number of doses per secondary container. Any storage conditions should be clearly noted, using symbols for markets where English is not spoken (TRS revisions).
Delivery devices		<ul style="list-style-type: none"> The use of novel delivery devices that reduce risk of contamination are encouraged. Vaccines in prefilled injection devices should have both space-saving and auto-disabling features (i.e., be compact, prefilled auto-disable devices or CPADs). CPADs (e.g., UniJect®), which offer advantages and savings over vials and syringes in terms of dose accuracy, ease and speed of preparation, and decreased disposal volume, and are encouraged. (VPPAG-gPPP)
Labelling **Planned for transition to critical criteria in next revision	All vaccines	<ul style="list-style-type: none"> Primary and secondary containers should be labelled according to the principles set out in the proposed amendments to TRS 822, including: <ul style="list-style-type: none"> For primary packaging, the following information should be included on the label: Product name (generic and brand), antigen abbreviation, doses per container, storage indications (damaged by freezing, if applicable), route of administration, intended age range, batch number, manufacturer name, expiry date (TRS revision). For secondary packaging: the printing on all three non-opposing faces of the carton should indicate at least the following information: Product name (generic and brand), antigen abbreviation, doses per container, storage indications (damaged by freezing, if applicable), route of administration, intended age range, batch number, manufacturer name, expiry date (TRS revision).
Barcodes **Planned for transition to critical criteria in next revision		<ul style="list-style-type: none"> Bar codes are recommended on all packaging levels used by manufacturers, with the exception of primary packaging, and should conform to GS1 standards and associated specifications. Bar code data should include the Global Trade Item Number (GTIN), lot number, and expiry date.(VPPAG)

4.4.1 Vaccines still in development

For vaccines still under development, the preferred characteristics noted above should serve as guidance to manufacturers on the minimum desirable standards that should be aimed for and tested against. It is recognized that the WHO TRS for some developmental vaccines are not yet finalized and are continuously updated.

More detailed guidance on ideal product characteristics for vaccines still in clinical development can be found in the following:

- The generic Preferred Product Profile (gPPP), was developed as a consensus document by the Vaccine Presentation and Packaging Advisory Group (VPPAG), a joint public sector and industry group. This paper provides recommendations for vaccine producers and developers on presentation and packaging of new vaccines for use by public-sector programmes in developing countries. Parameters include recommendations on areas such as temperature stability, anti-microbial preservatives, product format and optimal doses per vial. To access the gPPP please visit: <http://www.who.int/immunization/policy/committees/vppag/en/index2.html>.
- WHO Preferred Product Characteristics (PPC) aim to drive early stage research to develop new products or improve existing ones in a highly strategic way to meet the public health need focusing in particular on low and middle income countries. For information on PPC's in relation to vaccines please consult: http://www.who.int/immunization/research/vaccine_preferred_product_characteristics/en/

Please note that both this documents are updated regularly and manufacturers are encouraged to check the aforementioned webpages for updates.

5. The process of screening vaccine candidates before evaluation of the Product Summary File (PSF)

In order to avoid the resource- and time-consuming process of PSF evaluation for vaccine candidates that are not in compliance with programmatic suitability characteristics, the characteristics identified here will be screened by the PQ Secretariat, with the support of the PSPQ Standing Committee, as applicable, before evaluation of the PSF. The screening process has two objectives:

- to assess compliance with mandatory and critical characteristics;
- to identify other unique and innovative characteristics and assess their acceptability.

The PQ Secretariat screening process is shown in Figure 2 on page 19.

After it is determined that a vaccine is a PQ priority*, vaccine candidates will be screened for compliance with the mandatory characteristic values. If screening reveals that mandatory characteristics are not met, then the submission will be rejected.

If there is compliance with mandatory characteristics, then the PQ Secretariat will assess critical characteristics and identify unique and innovative characteristics. Critical characteristics are important but, in the case of deviation, allowance is given for recommendations from the PSPQ Standing Committee. If identified, unique and innovative characteristics should also be assessed by the PSPQ Standing Committee.

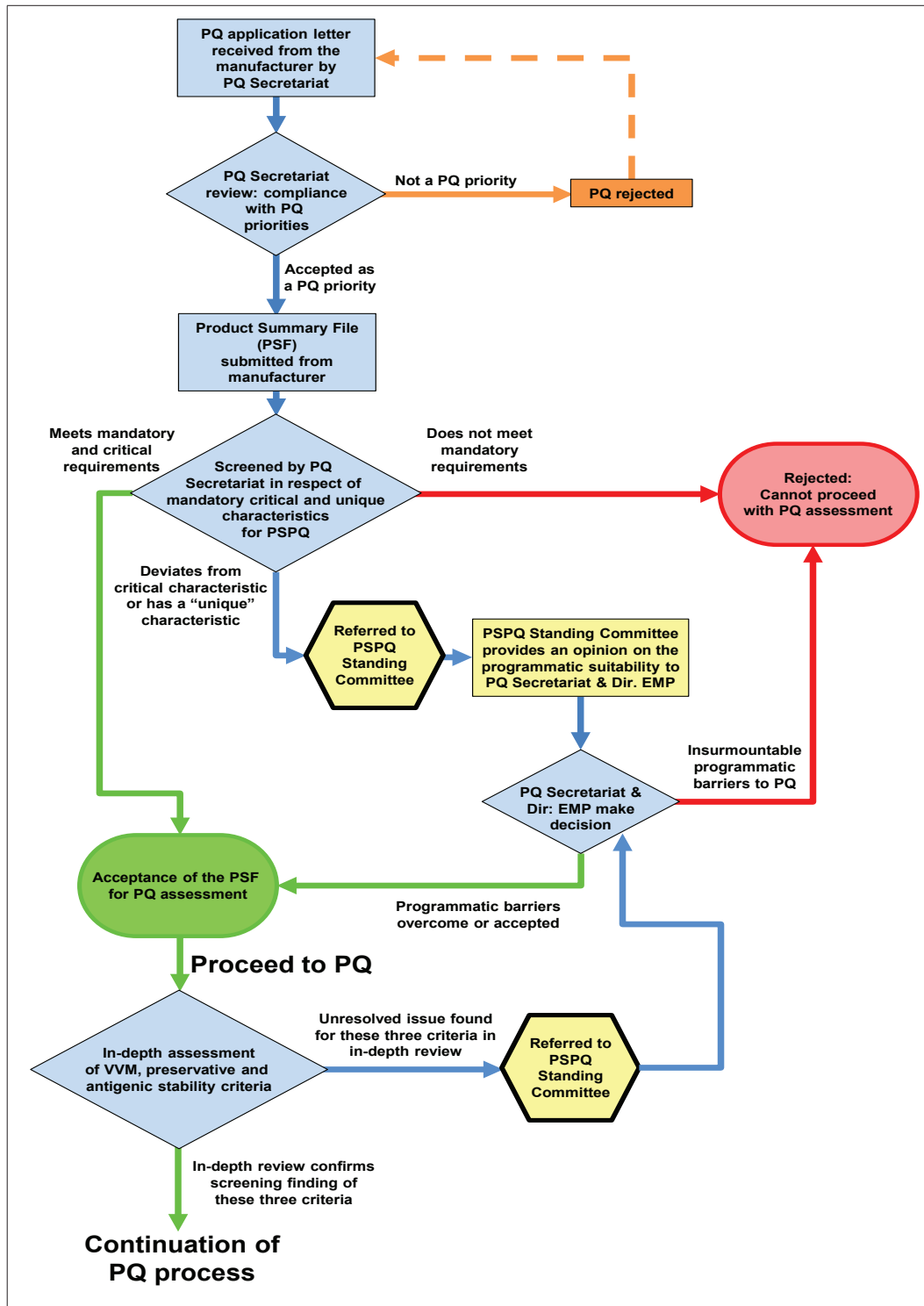
While all PSPQ criteria will be screened and evaluated initially, there are two critical criteria outlined in section Critical characteristics which will be reviewed again in more depth at the beginning of the PQ assessment (i.e. the formal PSF evaluation). They are as follows:

- vaccine vial monitor (VVM);
- anti-microbial preservative (absence, reduced concentration thiomersal or alternative preservative).

If, during this in-depth assessment, a deviation from the criteria is found that was not recognized earlier during the screening, then the vaccine will be referred back to the PSPQ SC for a second time. It is therefore possible that a vaccine which had been screened and had proceeded to the full PQ assessment is sent back to the PSPQ SC during the PQ assessment based on the in-depth review of the above two criteria. The PSPQ SC will have the same time to review the findings (i.e., three months) and it may recommend that further PQ assessment is suspended or ceased (see Figure 2 on page 16).

* http://www.who.int/immunization_standards/vaccine_quality/pq_priorities/en/.

Figure 2: Process for screening WHO prequalification documents to determine programmatic suitability of the vaccine



As noted above, under special circumstances when there is limited access to a vaccine of public- health importance, applications for vaccine candidates that are non-compliant with critical characteristics may be granted approval for evaluation of the PSF by the WHO PQ Secretariat and the Director EMP.

The decision to grant approval can only be taken by the PQ Secretariat and Director EMP and will include consideration of recommendations from the PSPQ SC and any additional issues. The public-health impact, both globally and regionally, of not pre-qualifying a vaccine will also be taken into consideration in the final decision. To reiterate: the referral for review of programmatic suitability by the Standing Committee of any given vaccine implies neither rejection nor clear acceptance for prequalification. The review of the Standing Committee is thus put into place to allow human judgment on these vaccine features after the vaccine manufacturer's representation and to make a recommendation of this to the PQ Secretariat and the Director EMP.

5.1 The PSPQ Standing Committee

An important element of the screening process is the support provided by the PSPQ Standing Committee (see Appendix 1: Terms of Reference: Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) Standing Committee).

The PSPQ Standing Committee serves as the main advisory body to the WHO PQ Secretariat and to the Director EMP on 'the suitability of the vaccine for the immunization services where it is intended to be used' (p.6, WHO/IVB/05.19⁴) in order 'to ensure that vaccines used in national immunization services in different countries ... meet particular operational specifications for packaging and presentation' (p.1, WHO/IVB/05.19⁴).

The PSPQ SC mandate is to provide recommendations and technical advice, and to assist the WHO PQ Secretariat and Director EMP to make informed decisions based on information provided by manufacturers, the input of external technical experts and other resources. Once the Director EMP has made the decision on PSPQ, the PQ secretariat should inform the vaccine manufacturer, the chair of the PSPQ SC and the WHO/HQ/IVB programme of the final decision.

The PSPQ SC advises the WHO PQ Secretariat and the Director EMP:

- on the programmatic suitability of vaccine candidates that are non-compliant with critical characteristics;
- on the programmatic suitability of vaccine candidates that present with unique and innovative characteristics.

The recommendations of the PSPQ SC will be based on information provided by manufacturers, the input of approved external technical experts, supply information from procuring agents and public-health needs.

The maximum allowed time for review by the PSPQ SC is three months. During a PSPQ SC review, the time clock for the PQ assessment process will be stopped.

6. Procedure for consultations requested by vaccine manufacturers before submission of an application for WHO prequalification

For discussion and interpretation of characteristics not described in the PSPQ paper, a vaccine manufacturer should contact the PQ Secretariat. The PQ Secretariat will identify a focal point who will arrange for a discussion between the manufacturer and the WHO PQ Secretariat. WHO may include the PSPQ SC in these discussions.

In this context, vaccine manufacturers may desire to request pre-application discussions with the WHO PQ Secretariat on prioritized vaccine candidates, or other vaccine candidates of public-health importance that:

- are non-compliant with mandatory characteristics;
- are non-compliant with critical characteristics;
- have unique and innovative characteristics.

As is the case with the application review process described above, the maintenance of confidentiality before, during, and after discussions is expected from all participants.

Although official minutes will be issued to all parties participating for the record of these discussions, the outcomes of the discussions are not binding on the WHO PQ Secretariat at the point of the prequalification assessment.

7. Implementation of the PSPQ requirements

7.1 Timeline for implementation of the revised PSPQ

PSPQ was initially implemented in January 2012. These revised PSPQ guidelines come into effect on 1 January 2015. As a result of this:

- 1) Any vaccine newly submitted for prequalification on or after January 2015 will be required to conform to these revised PSPQ guidelines as part of WHO's prequalification process.
- 2) Vaccines that were submitted for prequalification between 1 January 2012 and 1 January 2015 will not be required to be re-evaluated against these revised criteria in this version of PSPQ.

Vaccines that had received WHO prequalification prior to January 2012 and do not comply with these revised critical or mandatory characteristics will be reviewed by the PSPQ SC in 2014, and the relevant manufacturer informed. If the Standing Committee report recommends that the non-compliance makes the product unsuitable for continued prequalification, the PQ Secretariat will contact manufacturers and discuss, on a one-on-one basis, the concerns identified and the changes required in order to bring the product into compliance, along with a negotiated time frame to do so. The process will ensure that manufacturers have a fair chance and sufficient time to make the vaccines comply with PSPQ requirements. However, if an agreement cannot be reached with a manufacturer regarding a timeline for bringing a product into compliance with PSPQ criteria, or if the manufacturer does not comply with PSPQ requirements within the timeline negotiated and agreed upon, the product may then be removed by the PQ Secretariat from the list of prequalified products. The decision will take into account the public-health impact, including the availability of sufficient alternative products that meeting the programmatic needs of countries.

7.2 Procedure for changes to PSPQ process and criteria

The PSPQ process and criteria will be reviewed at a minimum every three years by the PQ Secretariat in consultation with the PSPQ Standing Committee, IVB team and the WHO regional offices. Expert input will be requested, as needed.

Any proposed changes will be presented to IPAC for endorsement, along with a proposed timeline for compliance with the new characteristics for both new, and already prequalified, products. The timeline for implementation will vary on a case-by-case basis, depending on the magnitude of the change. IPAC will be asked to endorse both the new or modified criteria, as well as the timeline for its implementation. Changes will not come into effect until after they have received IPAC endorsement.

However, should the criteria need to be changed to address issues of safety, the PQ Secretariat reserves the right to implement these changes with immediate effect, and without further consultation. Products that do not comply with changes to the PSPQ criteria implemented in order to address safety concerns will have their prequalification status withdrawn with immediate effect.

8. Summary and conclusions

After a review of WHO policy, and technical guidance and other sources, four mandatory and eight critical vaccine characteristics were identified. Also identified was a process for the review of unique and innovative characteristics that are not already identified as mandatory or critical. Characteristics that are preferred, but not yet considered as mandatory or critical, were also identified.

These characteristics are to be used in a screening process, which is intended to avoid the resource- and time-consuming process of formal PSF evaluation for vaccine candidates that are not in compliance with programmatic suitability characteristics.

It is expected that, in an effort to maintain an up-to-date document, characteristics will be updated by the PQ Secretariat when new or updated WHO policies and guidance becomes available. It may also be updated based on experience and lessons learned from evaluating characteristics, especially those that are unique and innovative.

Programmatic suitability characteristics can vary by WHO region, and it is expected that this variation will be expressed in the procurement and tendering process.

9. References

- 1) Malaria Vaccine Initiative. Public-sector preferences for RTS,S/AS01 malaria vaccine formulation, presentation, and packaging. October 2008.
- 2) Advance Market Commitment (AMC) for pneumococcal conjugate vaccines. Part I: Target Product Profile (TPP) for the Advance Market Commitment (AMC) for pneumococcal conjugate vaccines: Master table (<http://www.gavi.org/Library/Documents/AMC/TPP-Master-Table/>, accessed April 2010)
- 3) Vaccine Presentation and Packaging Advisory Group (VPPAG). Generic preferred product profile (gPPP), v2.1 AUG09 (<http://sites.google.com/site/vppagp/gppp>, accessed April 2010).
- 4) WHO/IVB/05.19. Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. Geneva, World Health Organization, 2005 (<http://www.who.int/immunization/documents/en/>, accessed April 2010).
- 5) Procedure for Assessing the Acceptability, in Principle, of Vaccines for Purchase by United Nations Agencies. WHO Expert Committee on Biological Standardization, Sixty-first Report; WHO Technical Report Series No. 978, 2013, Annex 6
- 6) European Pharmacopoeia 7th edition, section 5.1.3 Efficacy of Antimicrobial Preservation, pg. 505ff
- 7) WHO recommendations for routine immunization - summary tables (http://www.who.int/immunization/policy/immunization_tables/en/index.html).
- 8) WHO/IVB/06.10. Temperature sensitivity of vaccines. Geneva, World Health Organization, 2006 (<http://www.who.int/immunization/documents/en/>, accessed April 2010).
- 9) WHO/IVB/07.04. WHO-UNICEF policy statement on the implementation of vaccine vial monitors: the role of vaccine vial monitors in improving access to immunization. Geneva, World Health Organization, 2004 (<http://www.who.int/immunization/documents/en/>, accessed April 2010).
- 10) WHO/V&B/99.25. Safety of injections — WHO-UNICEF-UNFPA joint statement on the use of auto-disable syringes in immunization services. Geneva, World Health Organization, 1999 (<http://www.who.int/immunization/documents/en/>, accessed April 2010).
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- 12) WHO/IVB/05.23. Guidelines on the international packaging and shipping of vaccines. Geneva, World Health Organization, 2005 (<http://www.who.int/immunization/documents/en/>, accessed April 2010).
- 13) http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_manufacturers_guidance/en/index.html

10. Appendices

10.1 Appendix 1: Terms of Reference: Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) Standing Committee



Background

In the context of the World Health Organization (WHO) procedure for the prequalification (PQ) of vaccines for procurement by United Nations agencies, the WHO PQ Secretariat will assess 'the suitability of the vaccine for the immunization services where it is intended to be used' (p.6, WHO/IVB/05.19⁴). This is part of the broader process intended 'to ensure that vaccines used in national immunization services in different countries ... meet particular operational specifications for packaging and presentation' (p.1, WHO/IVB/05.19⁴).

Recently, the emergence of unique vaccine presentations and the expectation that innovation will continue into the future have driven the need to explicitly define the characteristics that determine programmatic suitability and the process for assessing compliance with these characteristics. WHO is committed to providing guidance to industry, and transparency and objectivity to the WHO decision-making process, of what is a programmatically suitable vaccine for PQ purposes (see Assessing the programmatic suitability of vaccine candidates for WHO prequalification). In addition, WHO would like to use this process to indicate vaccine characteristics that will not impact on the PQ process, but are identified as preferred characteristics.

As part of this procedure, it is expected that, for some PQ applications, the WHO PQ Secretariat will require support from an independent advisory group which will be referred to as the Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) Standing Committee.

Roles and responsibilities

Within the context of the WHO procedure for the PQ of vaccines for procurement by UN agencies, the PSPQ Standing Committee (PSPQ SC) acts as an advisory body to the WHO PQ Secretariat and the Director EMP. The WHO Dept. of Immunizations, Vaccines and Biologicals (IVB) supports this process through the development of these PSPQ guidelines, and the interaction with the PQ Secretariat and the PSPQ SC on specific programmatic questions.

The PSPQ SC mandate is to provide, on request, recommendations and technical advice on the programmatic suitability of vaccine candidates:

- that are non-compliant with critical characteristics;
- that present with unique and innovative characteristics.

The recommendation being sought is either:

- acceptance of the application to be further reviewed for prequalification; or
- rejection of the application. (In rejecting an application, the PSPQ SC may include a recommendation for resubmission after validation, by research, of the acceptability of specific characteristics).

The PSPQ paper listing mandatory, critical and preferred characteristics should be used for guidance (see earlier in this document).

The recommendations and technical advice of the PSPQ SC will be based on information provided by manufacturers, the input of external technical experts and public-health need.

Recommendations of the PSPQ SC are not binding on the PQ Secretariat or Director EMP.

The PSPQ SC has no executive, regulatory or decision-making function.

Membership

The PSPQ SC consists of five members.

- One member should have expertise in the management of developing country immunization programmes;
- one member should have regulatory expertise relating to vaccines used in developing country immunization programmes;
- two or three members will be designated from the WHO Immunization Programme Advisory Committee (IPAC).

PSPQ SC members shall serve in their personal capacity.

A public call will be issued for nominations for the remaining two or three non-IPAC positions in the PSPQ Standing Committee. Nominations will be received and selection will be made by an independent selection panel assembled by the PQ Secretariat. The three IPAC positions will be selected from nominations from the IPAC membership (excluding observers). Selections for both non-IPAC and IPAC positions will be based on qualifications and ability to contribute to the accomplishment of PSPQ SC objectives. Final approval of selections will be made by the PQ Secretariat and Director EMP.

Prior to taking up their responsibilities for WHO, PSPQ SC members will be required to complete a WHO Declaration of Interests form and a WHO Confidentiality Agreement. A register of members' Declaration of Interest forms and Confidentiality Agreements will be maintained by WHO.

Membership in the PSPQ SC may be terminated for any of the following reasons:

- failure to respond to two consecutive requests for reviews;
- change in affiliation resulting in a conflict of interest;
- lack of professionalism including, for example, a breach of confidentiality.

Term

All PSPQ SC members will be appointed to serve for a term of three (3) years. For the PSPQ SC members from IPAC, their terms will end when their IPAC membership ends, or when the PSPQ SC term ends, whichever comes first. After leaving IPAC, former IPAC members are eligible to be nominated and serve in either of the non-IPAC positions. Standing Committee members can be reappointed once and can serve a maximum of two terms.

Chair

A PSPQ SC Chair will be selected and appointed for one year by the PQ Secretariat and Director EMP from among the PSPQ SC members. The Chair is eligible to be reselected for appointment in the years following. The chair may also serve as a reviewer.

The Chair is responsible for:

- managing communications with the PQ Secretariat and Director EMP;
- managing the review process and approving all Standing Committee official records;
- appointing primary and secondary reviewers;
- assuring compliance with time frames;
- appraising if a previous PSPQ SC recommendation has been made on a vaccine with the same characteristics to determine the appropriate committee review process;
- submitting the final recommendations to the Director EMP;
- approving any publications based on these records;
- updating the paper *Assessing the programmatic suitability of vaccine candidates for WHO prequalification*, as appropriate.

Modus operandi

Schedule of PSPQ Standing Committee activities

PQ Secretariat requests to the PSPQ SC for recommendations and technical advice will be scheduled within two weeks of each submission deadline for PQ applications. Currently, the deadlines are as follows¹³:

- 31 January, 31 May and 30 September;
- specifically for seasonal influenza vaccines — July and November.

Communications between the PQ Secretariat and PSPQ SC may take place at other times during the year, as needed.

Management of communications between the PQ Secretariat and the PSPQ Standing Committee

A focal point, designated by the PQ Secretariat, will manage all communications between the PQ Secretariat and PSPQ SC and will, in the case of a request for a recommendation or technical advice, monitor and support the review process.

Within two weeks of each PQ submission deadline, and as otherwise needed, the designated focal point will contact the PSPQ SC Chair and provide a summary of applications that are to be reviewed, the reason for review, and the expected timeline for their completion (a maximum of three months after the initiation date).

For each review the focal point will:

- provide the PSPQ SC Chair with the relevant section of the vaccine candidate product summary file (PSF);
- communicate to the vaccine manufacturer that the application will be reviewed by the PSPQ Standing Committee, the reason for the review, and the expected timeline for completion;
- monitor progress, with the PSPQ SC Chair, of each review and facilitate use of a standardized review coversheet template;
- facilitate confidential communications with the manufacturer;
- facilitate the process of approval by WHO and the manufacturer of external technical experts to be consulted confidentially;
- collect and register WHO Declaration of Interests forms and a WHO Confidentiality Agreement from approved external technical experts;
- facilitate confidential communications with approved external technical experts;
- collect a second draft review from the PSPQ SC Chair and facilitate any discussion of the draft between the PQ Secretariat and the PSPQ Standing Committee;
- collect the dated final review from the PSPQ SC Chair, deliver it to the PQ Secretariat, and formally close the review.

Procedure for review of a vaccine candidate for WHO prequalification by the PSPQ Standing Committee

The maximum time allowed for review by the PSPQ SC is three months. During a PSPQ SC review, the time clock for the PQ process will be stopped. The recommendations of the PSPQ SC will be based on information provided by manufacturers, the input of approved external technical experts and public-health need. The primary and secondary reviewer should indicate to the PQ Secretariat as soon as possible if further information is needed. All material presented to the PSPQ Standing Committee, which may include unpublished material or documents from commercial entities, must be treated as confidential.

The review procedure (see Figure 3 on page 28) will as follows:

- The PSPQ SC clock to measure its timeline will be started when the relevant documents are made available to the PSPQ SC on the shared server, and when the chair is informed;
- The chair communicates the information regarding the vaccine to be reviewed to all PSPQ SC members, and then assigns one primary and one or two secondary reviewers.
- The outcome of this initial review by the primary and secondary reviewers is sent to the chair to be posted on the shared server for comments by entire PSPQ SC and PQ Secretariat. At the first presentation of the draft review, the primary and secondary reviewers will communicate to the PSPQ SC a clear recommendation for acceptance or rejection of the vaccine candidate and a summary justification for the recommendation.
- Once comments are received, the reviewers generate a final recommendation, unless there is disagreement among the reviewers which must be addressed by a teleconference.
- For vaccines where vaccine supply and availability is taken into account in formulating the PSPQ SC recommendation, the formal input from UNICEF SD and the PAHO Revolving Fund should be sought on the supply and availability of similar vaccines through the PQ Secretariat.
- In the case of disagreement among reviewers, discussion of the draft review will be led by the Chair with the objective of reaching consensus in the PSPQ Standing Committee. All PSPQ SC members need to participate and provide their opinion of the recommendation. When a simple majority, i.e., three of five members agrees on a recommendation, it will become the position of the PSPQ Standing Committee. Dissenting opinions should be included in a separate section of the draft review.
- When discussion is completed and incorporated into the draft review, a dated final review will be drafted by the primary reviewer and presented by the Chair to the PQ Secretariat, who will record the date of delivery and formally close the review. The agreed final recommendations are sent back to the chair and formally sent to the Director EMP as PSPQ SC recommendation.

The review should be conducted with specific reference to ‘the suitability of the vaccine for the immunization services where it is intended to be used’ (p.6, WHO/IVB/05.19⁴) in order ‘to ensure that vaccines used in national immunization services in different countries ... meet particular operational specifications for packaging and presentation’ (p.1, WHO/IVB/05.19⁴). The paper Assessing the programmatic suitability of vaccine candidates for WHO prequalification listing mandatory, critical and preferred characteristics should be used for guidance.

All vaccines that have critical or unique or innovative characteristics should be sent for review to the PSPQ SC. However, should the characteristics of the vaccine being sent for review by the PSPQ SC be the same as the characteristics of a vaccine that the PSPQ SC had previously reviewed and made recommendations on, the chair of the PSPQ SC in consultation with the committee may decide:

- to not conduct a further review of the presented vaccine;
- to provide the same recommendation to the Director EMP, citing the precedence of a previous decision.

The chair of PSPQ SC will maintain a list of characteristics and recommendations made by the PSPQ SC, and will indicate where a precedent recommendation was used to provide the recommendation to a newly submitted vaccine. This list will serve as record of the use of precedent decisions and should be reviewed when the PSPQ document is revised in three years again, for potential inclusion in the mandatory or critical criteria. There will be no public communication of PSPQ decisions or the use of precedence decisions, as in line with section 10.2 Appendix 2: Confidentiality and the public record of the PSPQ Standing Committee on page 29.

During a review, the PSPQ SC may engage in confidential discussions with manufacturers. The PSPQ SC may also engage in confidential discussions with external technical experts that have been approved by WHO and the manufacturer, and that have completed a WHO Declaration of Interests form and a WHO Confidentiality Agreement. Any requests for discussions with the manufacturer, or external technical experts, will be facilitated by the focal point and Chair, and should be made as soon after the review assignment as possible.

In addition to the final review, a standardized review coversheet template should be used to communicate the PSPQ SC recommendation (acceptance or rejection) and a summary justification. Additional administrative information should also be included in the template, such as: date of review assignment; the names of the Chair and primary and secondary reviewers; milestones such as the date of the first draft review by the PSPQ Standing Committee; the date of the second draft review by the PQ Secretariat, and the date of final review submission to the PQ Secretariat. The standardized review coversheet should be maintained by the lead reviewer, with support from the focal point and Chair.

10.2 Appendix 2: Confidentiality and the public record of the PSPQ Standing Committee

The final review and the review coversheet serve as the record of requests to the PSPQ Standing Committee, and their recommendations, and constitute the official record of the PSPQ Standing Committee. PSPQ SC official records are confidential and can be shared only with the PQ Secretariat and the Director EMP. The PQ Secretariat is responsible for sharing official records with the manufacturer that submitted the PQ application letter and associated PSF.

Publications based on the PSPQ SC official records can only be made with the explicit approval of the manufacturer, the PSPQ SC Chair, the PQ Secretariat and Director EMP.

Publications based on the PSPQ SC official records should be used to support and update the paper Assessing the programmatic suitability of vaccine candidates for WHO prequalification and inform policy and technical discussion in the vaccine community.

Procedure for consultations requested by vaccine manufacturers before submission of an application for WHO prequalification

For discussion and interpretation of characteristics explicitly described in the PSPQ paper, a vaccine manufacturer should contact the PQ Secretariat.

For discussion and interpretation of characteristics not described in the PSPQ paper, a vaccine manufacturer should contact the PQ Secretariat. The PQ Secretariat will identify a focal point who will arrange for a discussion between the manufacturer, WHO and the PSPQ Standing Committee.

In this context, vaccine manufacturers may wish to request pre-application discussions with the WHO PQ Secretariat on prioritized vaccine candidates, or other vaccine candidates of public-health importance that:

- are non-compliant with mandatory characteristics;
- are non-compliant with critical characteristics;
- have unique and innovative characteristics.

As with the application review process described above, the maintenance of confidentiality before, during and after discussions is anticipated from WHO, the PSPQ SC and other participants.

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