



**World Health
Organization**

**CLINICAL CONSIDERATIONS FOR EVALUATION OF
VACCINES
FOR PREQUALIFICATION¹**

Points to consider for manufacturers of human vaccines

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Vaccine, Quality and Regulation (VQR), Quality, Safety, and Standards (QSS)
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¹ These are derived from a WHO Workshop on PREQUALIFICATION PROCEDURES FOR VACCINES held in Chiang Mai, Thailand, 15 – 19 February 2010

1. INTRODUCTION

The United Nations Children's Fund (UNICEF) and other United Nations (UN) agencies take into consideration advice provided by the World Health Organization (WHO), through its Department of Immunization, Vaccines and Biologicals (IVB), on the acceptability, in principle, of vaccines considered for purchase by such agencies; this is known as vaccine prequalification. The procedure to assess such acceptability is described in the document WHO/BS/10.2155 (*Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies*). The procedure includes, for each product, the evaluation of the product summary file (PSF), initial testing of vaccine samples, and a WHO site audit. Part of the PSF evaluation is the evaluation of the clinical experience with the candidate vaccine, which is usually done by external reviewers contracted by WHO. These evaluators, whose names are agreed upon by the manufacturer of the candidate vaccine, make recommendations based on the available clinical evidence of efficacy, immunogenicity and safety for the product. These recommendations are taken into account by WHO in the decision-making process for prequalification of each individual product.

The clinical evaluation of vaccines for prequalification differs, in part, from that conducted by national regulatory authorities (NRAs), as WHO will have a broader view of any vaccine than any individual NRA, whose mandate is restricted to its own jurisdiction. Among other things WHO evaluates whether there is evidence to support the use of candidate vaccines according to the Expanded Programme of Immunization schedules, and takes into consideration morbidity and mortality of the disease to be prevented in different target populations where the vaccine is likely to be used if prequalified, the influence of local serotype or strain distribution on vaccine efficacy, and possible interference due to concomitant administration of other vaccines. In their reviews WHO evaluators focus on information that is not part of the NRA approval process, although in practice they also do at least a verification of what is expected to have been evaluated by the NRA.

Manufacturers have followed the guidance of document *Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies* (now revised as WHO/BS/10.2155), which refers to other complementary WHO guidance documents. However WHO Secretariat and evaluators have noted that interpretation of parts of those documents vary from one applicant to the other, and particularly new applicants have many doubts on the clinical requirements for prequalifying a vaccine. The submission of insufficient supporting clinical data has delayed, and sometimes prevented, the prequalification of products that are needed worldwide for the prophylaxis of vaccine-preventable diseases. Clarification of the requirements for the prequalification of vaccines additional to what is provided by existing WHO guidance documents was deemed necessary.

This document intends to provide additional guidance to manufacturers who submit applications for prequalification of vaccines. It includes some items that are included in the document WHO/BS/10.2155 (*Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies*). It shall be read in

conjunction with that document, and with TRS 924 (*Annex 1: WHO guidelines on clinical evaluation of vaccines: regulatory expectations*) and other relevant WHO documents.

2. SUBMISSION AND REVIEW PROCESS

2.1 Format and content of an application

The format of the application should follow the recommendations of the document WHO/BS/10.2155. Applications in the PSF format are required and it is acceptable that the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Common Technical Document (CTD) format (if available) be submitted. The PSF sections may be limited to detailed cross references to the relevant CTD sections simplifying the preparation and review of the application. The whole CTD instead of only the modules that are relevant to the clinical evaluation should be presented, since there are often internal cross-references in that document.

The PSF should now include in its chapter on Clinical experience (currently Chapter 8) the following additional requirements as stated in the document WHO/BS/10.2155:

- a) a tabulated summary of the Clinical development programme;
- b) a completed clinical trial model summary protocol (according to TRS No. 924, p. 95) for pivotal (often phase III) trials;
- c) details of entry into a clinical trial registry
- d) a pharmacovigilance plan.

More details are presented below.

2.2 Screening of applications

The PSF of a vaccine submitted for prequalification is expected to have complete information to support the efficacy, immunogenicity and safety of that product, and evidence that such information is applicable to populations where the vaccine is likely to be used if prequalified. The summary of the clinical development programme and the pharmacovigilance plan will be evaluated by WHO Secretariat at the screening stage, to ensure that the application is complete. Queries may be sent to the applicant at this stage, and the acceptance of the application for review will be conditional to satisfactory answers.

NOTE: In the case of traditional well established vaccines, a justification should be provided whenever the non-clinical information and/or clinical development programme do not comply with the requirements.

2.3 Requirement for additional non-clinical Information

The PSF requires the presentation of a summary table of non-clinical studies (WHO/BS/10.2155) that will have been assessed during clinical trial and license applications. Additional information on non-clinical studies can be requested by the clinical reviewers whenever necessary (e.g. in the case of novel adjuvants), and if this is anticipated by the applicant such information may be included in the application.

2.4 Clinical development programme

The applicant should provide in the PSF a tabulated summary of the clinical development programme, in one or more tables, in which critical parameters that may have changed during the clinical development should be mentioned (see example in Annex 1).

2.5 Requirement for the protocols of clinical trials that support the prequalification application

The applicant must provide the protocols of the clinical trials supporting the application in English and in the original language, if different. The protocols should be the final approved versions, incorporating all amendments.

2.6 Evidence of Ethics Committee approval of clinical trials

Evidence of approval of the clinical trials by competent Ethics Committees, as well as information about their contact details, are expected to be included in the PSF.

2.7 Evidence for Good Clinical Practices (GCP) conduct of each trial

In the absence of a certificate of GCP compliance from the responsible NRA, applicants should provide evidence of GCP compliance for each phase III trial, of the monitoring of the trial conduct by the sponsor (or contract research organization), audits by the sponsor, available NRA inspection reports, and data and safety monitoring board (DSMB) reports.

2.8 Evidence for registration of each clinical trial

Each clinical trial that supports a prequalification application (including phase IV trials) must have been registered in a registry that is included in the WHO International Clinical Trials Registry platform. The name of the registry and the registry number must be provided. If this is not possible the reason(s) should be explained.

2.9 Clinical trial end-point assays - relevance, validation and accreditation

It has been noted that in some clinical trials the assays used to determine immunogenicity end-points (including thresholds for seroconversion) have no evidence of relevance to the efficacy of the vaccine in question (e.g. specificity), and there is often no evidence of assay validation or standardization, or of the competence of the laboratory to conduct these tests.

The serological correlate of protection used in the analyses must be justified and supported with best scientific evidence available. Evidence should be provided of end-point immunogenicity assay relevance and standardization. Assay results should be reported in international units wherever possible.

The laboratory should be identified, and evidence of competence or accreditation to conduct these assays should be provided.

2.10 Independent Expert Reports

Independent expert reports are required for the PSF. Reports in the ICH CTD format (clinical overview and clinical summary) may be accepted where evidence is provided that these comply with the ICH requirements for expert reports.

2.11 Vaccine lots used in clinical studies and lot-to-lot consistency studies

Consistency of manufacturing for the vaccine lots used in clinical trials should be demonstrated and well documented. It is ideal that at least three lots with the same formulation intended for marketing are used in the late stages of the clinical development programme. However, a formal lot-to-lot consistency clinical study is considered only on a case-by-case basis, in particular when assessing vaccine formulations with inherent variability.

It is important to note that there are a number of important issues to consider in the event that the manufacturer decides to perform a lot-to-lot consistency clinical study to fulfil the requirements for vaccine licensure of a NRA. Vaccines used in clinical-consistency trials must have been manufactured at full production scale. The study should be designed (and analysed) as an equivalence trial and have a pre-defined criteria and choice of parameters to conclude comparability.

Changes to the batch size used to produce the clinical lots will require additional information to support the change (e.g. scale-up). Depending on the manufacturing consistency data, additional clinical studies to support comparability to the clinical lots may be required. These issues should be decided in consultation with the WHO Prequalification Secretariat.

2.12 Subject exposure to a new vaccine in clinical trials

For assessment of safety and immunogenicity it is expected that results from an adequate number of subjects, exposed to the vaccine, and monitored during comparative clinical trials will be provided for prequalification review. The sample of subjects should be enough to give the study a minimum of 80% statistical power to detect adverse events of concern that may occur at about 1:1000 incidence. The vaccine characteristics, the population under study and the study design should be considered to determine the number of the subjects evaluated in clinical trials. This needs not be a single clinical trial but could represent cumulative exposure across all clinical studies provided that the vaccine used in these studies is similar to and representative of the final formulation to be marketed.

In cases where vaccines had been licensed by NRAs based on small sample sizes and where there is insufficient supporting safety data e.g. in cases where vaccines are produced for export only and/or post-marketing surveillance is unreliable, phase IV studies may be requested by WHO so as to provide sufficient information on which to make a decision about the safety of the vaccine. .

2.13 Follow-up in clinical trials

It is expected that there will be a follow-up of at least 6-months in clinical trials after the last dose of the vaccine, for safety assessment. This should be active and not reliant on spontaneous reports.

For efficacy and immunogenicity assessment longer follow-up, of at least one year, may be expected depending on the clinical endpoint requirements. Applicants are directed to guidance documents on specific vaccines for further information.

Immunogenicity assessment before and after the booster dose will be required for vaccines given as a booster dose.

2.14 The use of placebo as comparator in vaccine clinical trials

This has become practically impossible and ethically unacceptable for trials of new vaccines for diseases where vaccines already exist. The relevance of the immunogenicity end-points depends on scientific evidence available to support the serological correlate or surrogate of protection for each particular vaccine and the use of relevant and validated assays. This evidence must be provided.

This is addressed in the section on relevance and standardization of immunological assays (see section 2.9).

2.15 Vaccines produced for export only

Applicants that produce vaccines for export only are faced with particular difficulties in collecting and collating safety data. In these cases manufacturers should consider the need to evaluate the safety and efficacy of the vaccine in different populations and disease backgrounds if the vaccines are intended for use in various regions and parts of the world supplied by donor agencies. These data must be presented at the time of pre-qualification application.

2.16 Consideration of quality of safety data from passive pharmacovigilance programs

The voluntary reporting systems in place in many countries do not function efficiently and in addition the inherent limitations of such systems such as under-reporting and the lack of a denominator in terms of the number of persons actually exposed to the vaccine make this information of limited value. If safety data from clinical trials and from passive pharmacovigilance systems are inadequate, not reliable or incomplete, results from a phase IV study will be required for prequalification evaluation.

2.17 Requirement for a pharmacovigilance plan as part of the PSF

Risk management plans, including pharmacovigilance plans, are part of modern risk management strategies required by stringent regulatory authorities. A Pharmacovigilance plan taking into consideration where the vaccine is likely to be used if prequalified is required as an essential part of the PSF.

2.18 Periodic Safety Update Reports (PSURs)

Provision for presentation of PSURs should be present in the Pharmacovigilance plan at the time of submission of the PSF. PSURs should be submitted annually for all vaccines.

2.19 Post-prequalification commitments

There should be sufficient clinical data submitted in the PSF or in responses to reviewer questions on which to decide on a recommendation for prequalification. Provisional prequalification of products with insufficient clinical data based on a post-prequalification commitment to provide additional data should not be accepted.

1 **ANNEX 1 CLINICAL DEVELOPMENT PROGRAMME: CHARACTERISTICS OF CLINICAL VACCINE LOTS USED IN**
2 **CLINICAL STUDIES.**

3 **Table 1: Changes to the manufacturing process or to the formulation of lots used in clinical studies**
4

Parameters	Final Commercial Formulation	Clinical Study					
		No. 123 Phase 1	No. 234 Phase 2	No. 345 Phase 2	No. 456 Phase 3	No. 567 Phase 3	No. 678 Phase 3
Batch size	1500 L	20 L	20 L	20 L	20 L	20 L	1500 L
Manufacturer of intermediates (facility location)	Best Vaccine LTD, Geneva	GoodVac LTD, NY	GoodVac LTD, NY	GoodVac LTD, NY	GoodVac LTD, NY	Best Vaccine LTD, Geneva	Best Vaccine LTD, Geneva
Formulation facility	Best Vaccine LTD Rio de Janeiro	GoodVac LTD, NY	GoodVac LTD, NY	GoodVac LTD, NY	GoodVac LTD, NY	Best Vaccine LTD, Geneva	Best Vaccine LTD Rio de Janeiro
Excipient(s)	Albumin	No Albumin	No Albumin	Albumin	Albumin	Albumin	Albumin
Preservative	Thiomersal	No thiomersal	No thiomersal	No thiomersal	No thiomersal	thiomersal	thiomersal
Vaccine presentation	Multidose (10 ml)	One dose	One dose	One dose	One dose Syringe	One dose Syringe / multidose	multidose
Concentration / composition of antigen or adjuvant	PS type Z (10 µg) Carrier prot-6 (5 µg) w/o emulsion + Immstim® (2 µg)	PS type Z 5 µg Carrier prot-6 Alum	PS type Z 20, 10, 5 µg Carrier prot-6 Alum	PS type Z 10 µg Carrier prot-6 Alum + Immstim® (2 µg)	PS type Z 10 µg Carrier prot-6 Alum or w/o emul + Immstim® (2 µg)	PS type Z 10 µg Carrier prot-6 w/o emulsion + Immstim® (2 µg)	PS type Z 10 µg Carrier prot-6 w/o emulsion + Immstim® (2 µg)
Others.....							

5 The above table should include critical parameters that may have changed during the
6 clinical development of a particular vaccine. The table is an example of potential
7 changes to the manufacturing process or to the formulation of a vaccine during clinical
8 development.