



Guideline for preparation of the product summary file for vaccine prequalification

The World Health Organization has managed cooperation with its Member States and provided technical support in the field of vaccine-preventable diseases since 1975. In 2003, the office carrying out this function was renamed the WHO Department of Immunization, Vaccines and Biologicals.

The Department's goal is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. Work towards this goal can be visualized as occurring along a continuum. The range of activities spans from research, development and evaluation of vaccines to implementation and evaluation of immunization programmes in countries.

WHO facilitates and coordinates research and development on new vaccines and immunization-related technologies for viral, bacterial and parasitic diseases. Existing life-saving vaccines are further improved and new vaccines targeted at public health crises, such as HIV/AIDS and SARS, are discovered and tested (Initiative for Vaccine Research).

The quality and safety of vaccines and other biological medicines is ensured through the development and establishment of global norms and standards (Quality Assurance and Safety of Biologicals).

The evaluation of the impact of vaccine-preventable diseases informs decisions to introduce new vaccines. Optimal strategies and activities for reducing morbidity and mortality through the use of vaccines are implemented (Vaccine Assessment and Monitoring).

Efforts are directed towards reducing financial and technical barriers to the introduction of new and established vaccines and immunization-related technologies (Access to Technologies).

Under the guidance of its Member States, WHO, in conjunction with outside world experts, develops and promotes policies and strategies to maximize the use and delivery of vaccines of public health importance. Countries are supported so that they acquire the technical and managerial skills, competence and infrastructure needed to achieve disease control and/or elimination and eradication objectives (Expanded Programme on Immunization).

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Immunization, Vaccines and Biologicals



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Immunization, Vaccines and Biologicals



**World Health
Organization**



GAVI ALLIANCE

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Introduction

The WHO document “Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies” (WHO/IVB/05.19) explains the procedure followed by WHO under their mandate to provide an evaluation of the manufacturing and regulatory control of vaccines to UN agencies that wish to purchase these vaccines.

As defined in the text of the WHO document:

“the product summary file (PSF) is a brief (1-2 volume) summary dossier containing current information on the product to be supplied to UN agencies. It presents information on the product composition, manufacturing procedure, testing, stability, labelling, clinical experience, and available post-marketing safety information.

For initial product assessments, a product summary file shall be submitted for each vaccine to be assessed. For combination vaccines, information shall be submitted on each of the component vaccines and on the combination itself. If a combination vaccine is being evaluated and the monovalent versions of the antigens contained in the combination are also being evaluated, the information provided for the monovalent vaccines (up to concentrated bulk) can be used for the assessment of the combinations, or conversely, the information on each antigen provided in the PSF of the combination vaccine can be used to assess the monovalent vaccines (up to concentrated bulk level).”

The Pre-Qualification procedure document includes an Annex (# 1) which provides a brief outline of the topics expected to be in the PSF.

This new guideline provides further clarification of the information requested and general instructions on the content and recommended format for the PSF. This includes instructions for the preferred method for incorporating information from the Common Technical Document (CTD) format into the PSF.

This guideline lists the chapter titles and subchapter headings as given in Annex 1, with additional explanation or clarification of the expected information and contents.

General instructions

The PSF should be prepared in separate chapters using the chapter title and subchapter headings following the WHO format as given in Annex 1 of the WHO Procedure document WHO/IVB/05.19.

The PSF should have all pages numbered and each chapter tabbed for easy review. Tabs for the subchapters are optional.

The PSF should have a Table of Contents listing the chapters, subheadings, appendices and the corresponding volumes and page numbers.

For every chapter, each subheading should be followed by the information requested in this guideline (below). WHO accepts information for the PSF formatted in the CTD format (e.g. CTD Quality 3 Module). However, it is requested that the CTD module(s) be attached as an appendix (or in the case of combination vaccines, Appendices) to the PSF. Appendices should be in a separate volume for ease of reference during the review of the PSF document. Under each subheading in the PSF for which CTD information is provided, a cross-reference to the Appendix with the CTD information covering the topic should be given. The cross-reference should include the Appendix number, the CTD section title, the CTD page number, and any other relevant information for the reviewer. As the CTD gives complex page codes rather than sequential numbers it is recommended that the CTD module be stamped with consecutive numbers and these used for the cross-references.

In the case of combination vaccines, or for multiple presentations of a vaccine, or for separate formulations of the same vaccine where specific information is different, several chapters may need to be divided in the PSF. Chapter 5 “Production” (5.1 to 5.5) is recommended to be repeated for each bulk component, for formulation and filling, and, in the case of separate vials for combination vaccines mixed at the time of administration, for the reconstituted vaccine. For example: for DTP: Chapter 5A: Diphtheria bulk concentrate production; 5B: Tetanus Bulk Concentrate production; 5C: Pertussis pooled harvest production; 5D: formulation and filling – each with all the subheadings. If the differences are related only to one or several specific subheadings of a chapter, the subheadings can be duplicated (e.g. Composition 4.1A, 4.1.B) under a single Chapter 4. The Table of Contents page should clearly show these chapters.

If the PSF for more than one vaccine is submitted at the same time for pre-qualification (eg, Tetanus vaccine and DTP vaccine) containing one or more of the same antigens, subsections of chapters that are identical can be cross-referenced to the other PSF.

The manufacturer is advised to contact WHO staff before the submission to discuss the details.

All WHO format chapter titles and section subheadings should be included in the PSF. If a chapter subheading is not applicable, it should NOT be deleted, but included as “not applicable” with an explanation if necessary. In chapters where the CTD provides most of the information (eg Production, Quality control, Stability) by cross-reference (see above), any additional information requested by WHO in that chapter should be included under the PSF chapter subheading (see figure 1).

Figure 1: Example
(WHO chapter and subheadings in red, responses in blue)

WHO Chapter 7: Stability
<p>Example 1:</p> <p>Section 7.1: Stability tests on intermediates:</p> <p>a) Assigned shelf life and storage conditions: See Appendix 1, Volume 2, CTD section 3.2.S.xxx, page yy and zz.</p> <p>b) QC methods and specifications and rationale for the choice of tests for determining stability; See Volume 2: CTD section 3.2.S.xxx, for the QC tests (pages y-y) and specifications (pages x-x). ii) Rationale for the choice of tests: (give full explanation here)</p> <p>c) Identification of the dates of manufacture of the lots, the lot numbers, the vial and dose size, and the scale of production; Either: See tables X,Y, Z in Volume 2: CTD section 3.2.S.xxxx, pages xx-xx) (or if not in the CTD list the lot numbers and id requested). Results of quantitative assays must be expressed as a numerical value with the appropriate limits and not as “pass” or “fail”. Either: See Table X, Y, Z in Volume 2: CTD pages x, y, z, (or provide additional information on the specific numerical values obtained.).</p>
<p>Example 2:</p> <p>Section 7.4 Description of the policy for assigning the date of manufacture of each component as well as the final product (e.g. combination vaccine) and diluents, as appropriate.</p> <p>As this is not included in the CTD module, provide this information under this WHO PSF subheading.</p>

Details and clarification of the contents of the PSF chapter sections

For each chapter and section, copied here from Annex 1 of the WHO prequalification procedure document, the subsequent boxed text provides the details of the information to be submitted.

Chapter 1: General Information:

- 1.1 Brief information on the firm (including name and address of the site, including telephone, fax and 24-hour telephone numbers, and the principal contacts of the Company), relation to other sites where steps of the process or testing activities may be conducted.

It is expected that the name of the company applying for PQ is listed first. The full address of the head office and contact person with his/her title/position, and the contact numbers should be given. This should be followed by a listing of other sites or other companies involved in any phase of production or testing, (parent company, other sites for the company, any contract manufacturers or testing laboratories, subcontracted warehousing, etc) and their addresses.

The relationship between sites is a request for an indication of generally how the product is transported between the various sites for production, testing and storage.

- 1.2 Pharmaceutical and non-pharmaceutical activities carried out at the site as licensed by the National Regulatory Authority. This information should be provided as well for contracted manufacturers.

A list of all licensed products made at each of the above mentioned sites should be provided. It is recommended to divide into lists of biologicals, pharmaceuticals and any other licensed products that the company or contract manufacturers produce. If licenses are required for R&D products or clinical product manufacture, please indicate these also.

- 1.3 Short description of site (size, location and immediate environment). List of buildings on the site(s), or a site plan, identifying the manufacturing, control, and storage activities in each building.

The site description, list of buildings, site plan, and activities in each building should be given separately for each of the sites listed in 1.1. If individual buildings have production suites for different products or if the production areas are used on campaign for different products, the description and list should clearly identify the products made in each building and/or area. If different steps of the production process are carried out in different buildings or sites for the product under review, they should be specified, including storage of intermediates, and storage of final product. Off-site warehouses should also be listed and how these storage locations are controlled.

1.4 Number of employees engaged in the production, Quality Control, storage and distribution.

The total numbers of employees in these departments is requested, as well as the numbers in the production of the specific vaccines under review. It is recommended to give QA and QC figures separately and to include the number of staff in the engineering/plant maintenance departments.

1.5 List of outside scientific, analytical or other technical assistance in relation to manufacture and analysis, including equipment, utilities and/or other facility maintenance and validation. In case of contract manufacturing and contract testing of part of the process, information on the way in which GMP compliance of the contract acceptor is assessed.

This section requests first a list of all the contracted employees or companies involved in production, testing or facility maintenance/validation (or qualification). In addition, for subcontracted testing or production, please provide a short description of the procedure the applicant company follows for auditing the GMP compliance of these subcontractors.

1.6 Short description of the quality management system of the firm responsible for manufacture.

Here, the request is to describe the overall procedures followed by the company as detailed in policy documents and in written SOPs (the titles and numbers could be listed) to ensure the quality of production and control.

1.7 Short description of the internal audit system and program for auditing suppliers of raw materials.

Provide information on the responsible department, the overall general policy, the titles and numbers of SOPs for internal audits, the frequency of internal audits, and the timing and follow-up for remedial action.

Chapter 2: Personnel

- 2.1 Organizational Chart showing relationships between different areas including Quality Assurance, production and Quality Control, with identification of the key personnel (Head of Production, QA, QC, Warehousing, Engineering).

A chart should be prepared for the overall management including all departments at the company, and also a chart for each department involved in production and control of the product under review: QC, QA, Engineering (plant maintenance), Warehousing and Distribution. The department responsible for training should be identified in these charts.

- 2.2 Qualifications, experience and responsibilities of key personnel

Key personnel are the heads of departments involved in the production, testing, warehousing/distribution of vaccines, QA, and the managers of the production of the vaccine under review. A CV (dated) of each is desirable or a table summarizing their qualifications, number of years in industry, number of years at the company, number of years in the current position, and their current responsibilities.

- 2.3 Outline of arrangements for basic and in-service training and how records are maintained.

Indicate what department is responsible for organizing training for staff: induction training, job training and GMP training, and the responsible departments for the actual training.

The types of documentation for such training (use of SOPs, guidelines, test materials) and the methods of evaluation of individuals employee's test results should also be described briefly. The topics and frequency of GMP training as well as upgrading training in instances of poor performance should be included

Information on the location of training records (e.g. in training files, in each employee's file) is requested. For production and QC procedures, indicate if a list of employees is maintained to identify those trained and approved to carry out the procedure or whether SOPs have a section listing trained operators.

Also provide general information regarding any training on equipment by the suppliers (specific operations or validation training).

- 2.4 Health requirements for personnel engaged in production, particularly relating to requirements for immune status for production personnel, and outside contract service personnel entering the manufacturing areas.

This should describe the general policy for the company for employees and contractors entering the production or testing areas where products are manipulated, as well as to details of the immunization of the production and QC staff involved in the production of the vaccine under review

Chapter 3: Premises and Equipment

These will be examined in depth during the site visit. However, the following preliminary information shall be submitted:

- 3.1 Simple, currently valid, dated floor plans and text description of manufacturing and quality control areas. The floor plans should give an indication of scale, airlocks, air flow and flows of materials, product, personnel and waste (architectural or engineering drawing are not required). RH, and room classifications. Air Handling Units (AHU) should be identified by room.

A composite, dated diagram (floorplan) identifying production rooms, entries, airlocks and pass-throughs, room numbers and activities, location of major equipment including laminar flow hoods (LFHs). Colour-coded arrows should be superimposed to show the flow of personnel, RM/supplies, product, and waste. Please ensure that the flow arrows indicate the actual personnel, RM and production flow for the product and not just general flows. If separate diagrams are given for the flows ensure that they are to the same scale so they can be compared.

Please provide a floorplan diagram for each facility/area involved in production of the product(s) under review, including diagrams for contract manufacturing facilities.

For QC laboratories, provide diagrams of the individual laboratories indicating any controlled areas (e.g sterility), LFHs, and the activities carried out in each room. For animal testing areas, provide a diagram of the rooms used, tests performed, the species kept in each room, and any controlled areas. (Details of the animal breeding or holding areas will be assessed during the site visit.)

Please ensure that if photocopies of existing drawings are submitted that they are large enough to read, that the legends are clear and that colour copies are provided if colour-coded arrows or markings have been used.

Text is to be provided to give a general description of the activities marked on the diagrams.

- 3.2 Nature of construction and finishes, of manufacturing and Quality Control areas.

This information is requested to give a sense of the quality of the premises. For production premises, the materials/ finishes for walls, ceilings and floors are expected to be such as to allow for cleaning, sanitization or sterilization procedures required for the purpose for which they are intended. The details provided should give an indication of the ease of cleaning between campaigns or after any unforeseen contamination. Ceiling construction and lighting access should be included for the various room classifications. Give a brief description of any technical floors servicing the production rooms.

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- 3.3 Description of ventilation systems in the manufacturing and Quality Control areas. More details should be given for critical areas with potential risks of airborne contamination (schematic drawings of the systems are desirable). Classification of the clean-rooms used for the manufacture of sterile products should be included. Description of environmental monitoring program is required.

A detailed description of the HVAC system is required including values for air pressure, air quality, temperature, and RH for each production room. Access for maintenance, monitoring and servicing HVAC systems should be indicated. A diagram, preferably at the same scale as in 3.1, should be prepared for each production area to show the location of the air intake and return ducts, HEPA filter location (e.g. terminal), arrows for air flow (or pressure values in each room and airlock). Each room should be marked with the dynamic classification, room number and activity. Specify the classification system used.

Exhaust air vents on roof should be described to show adequate separation from air intake to the facility.

The environmental monitoring programme description should include the frequency of particle and viable counting performed in the cleanrooms and connecting airlocks (dynamic and static conditions) for air, surfaces and personnel, sampling equipment and methods, temperature and RH monitoring and specifications, performance qualification (PQ)/ re-PQ schedule, and frequency of testing the HEPA filters and LFHs.

- 3.4 Special areas for the handling of highly toxic, hazardous and sensitizing materials.

If any such substances are used in production or in adjacent areas, indicate the locations and how these are controlled and/or segregated.

- 3.5 Description of water systems (schematic drawings of the systems are desirable showing storage tanks, loops, points of use, and sampling points) including sanitation procedures and schedules. Description of QC testing and schedules is required.

Provide a simple diagram of the site and simple floor plans of the facilities involved in production for the vaccine under review. On these please show where purified water and WFI are produced and how it is circulated to each building. Show storage tanks for WFI, WFI loops, and location of points of use (POU) for each loop in the cleanrooms, number of the POU's and identify those where sampling takes place, and those that are permanently connected to equipment. Simple diagrams – not engineering drawings are requested.

The specifications and tests methods and frequency for purified water should be presented. The method used for producing WFI and the system used for the sanitization of the WFI system should be described in detail giving the pharmacopoeial specifications followed; sanitization treatment used, frequency and qualification/validation and re-qualification/validation procedures.

A brief description of the sampling method and frequency of sampling/testing at each POU are requested.

3.6 Maintenance (description of planned preventive maintenance programmes and recording system).

This section should describe the scheduling of the routine checks and re-validations of critical production equipment and product contact equipment. The responsible department should be indicated as well as the types of records (equipment logs, SOP record sheets, etc) and procedures for maintaining these records. Explain how preventive maintenance is scheduled into the production schedule. It would be useful to indicate which equipment can be accessed from outside the production areas for maintenance.

3.7 A list and brief description of major production and control laboratories equipment.

A list of the equipment, use, type, and size would be appropriate. Indicate which equipment items are computer controlled.

3.8 For products where separate facility is required (e.g. tetanus, BCG) describe how separation is achieved.

Describe the physical separation of clean rooms, personnel separation, air / water separation, mobile equipment separation, glassware and other re-usable supplies, separation, and waste segregation.

3.9 Description of qualification and validation procedures, including computerized recording and controller systems. Description of the validation master plan is required.

Describe the procedures as performed at the company for the premises, utilities and equipment: initial qualifications/validations; re-qualification and re-validation policies and frequencies; identification of the procedures that are contracted out and the companies used. In addition to a brief description of company policy, this could be prepared as a list of the utilities and equipment and information on routine and special qualifications/validations.

The description of the Master Validation Plan should state the overall policy of the company as written in this document and also include the procedures covered in this document (ie equipment, utilities, processes, assays, etc), the document number and most recent revision date.

3.10 Brief description of the procedures for cleaning manufacturing areas and equipment, and for multipurpose areas, the system for cleaning and testing between campaigns

This should include the SOP numbers and titles for cleaning of all areas involved with the vaccine under review, the cleaning and decontamination agents used and rationale for their choice and rotation if appropriate, and the procedures followed for validation of these cleaning processes, and the requirements and frequency of revalidation of cleaning processes.

Campaign cleaning procedures for bulk manufacturing areas that are used for several products should be presented and the validations performed to demonstrate the removal of potential contaminants before approvals for changing campaigns. The SOP(s) should be listed.

Chapter 4: Vaccine composition, presentations and schedules

4.1 Composition of the product.

For each presentation, different formulation (if applicable), and for the separate components of combined vaccines (if applicable) provide a table of the quantitative composition of the vial and of each dose including all excipients, stabilizers, adjuvants, and the minimum titer of the vaccine antigen(s) per mL and per dose. For a lyophilized vaccine, provide the quantitative composition for the diluent and for the reconstituted vaccine.

4.2 Description of the presentations made available to UN agencies, including diluents (if applicable), combination products, forms, dose sizes, type of containers, VVM type used and descriptions of application devices (e.g. syringes) to be delivered with the vaccine, if applicable.

A table of the presentations listing the items indicated will be sufficient.

4.3 Recommended schedule and route of administration.

Indicate the information as provided on the package insert (leaflet) and give relationship to the dose, schedule and route of administration investigated during the pivotal clinical trials, and/or from long term documented use of the vaccine.

4.4 Samples of labels, boxes and package inserts to be used for UN agencies' supply in English. Samples of vials or ampoules of diluents and its corresponding labelling. French, Spanish, Russian and Portuguese versions need to be made available before supply to UN agencies starts.

For vaccines not previously supplied to UN agencies, draft copies or art works of labels, boxes and leaflets for the vaccine, diluent as applicable, and of both vaccine components in the case of separate vials that are combined at the time of administration, should be provided for review and comment by WHO. The WHO guidelines for labelling (WHO TRS 822 Annex 1, section 7) and WHO model inserts

should be consulted when preparing the drafts. (Revised versions 2005 posted on the WHO website: http://www.who.int/immunization_standards/vaccine_quality/model_inserts/en/index.html)

For re-assessment of vaccine(s) currently supplied to UN agencies, current copies of all language versions are requested. The proposed inserts should comply (as a minimum not contradict) with the updated WHO model inserts.

4.5 Sample of lot summary protocol (LSP) to be provided to UN agencies (to follow the WHO-recommended format).

For each presentation or formulation or for separate vials of vaccine components that are combined at the time of administration, draft copies of the LSP for UN agency supply for review and comment by WHO should be provided for vaccines not previously supplied to UN agencies.

When available, the LSP proposed by the WHO TRS may be used as a basic template.

Current copy(ies) of the LSP for re-assessment of vaccine/s currently supplied to UN agencies is requested.

In the case of vaccine produced from a bulk antigen that is already prequalified by another manufacturer, the LSP should also contain the complete information for each antigen used. (a copy of the WHO format LSP of the bulk antigen provided by the supplier is acceptable) along with the WHO LSP format of the formulated bulk/final product.

Chapter 5: Production*

5.1 Manufacturing formulae:

- a) For the production of each antigen in the vaccine (i.e., fermenter or culture volumes for each bulk batch size as applicable and typical bulk volumes per production run);
- b) The batching formula for each batch size of final formulated bulk product;
- c) The approximate number of vials and doses for each fill size and presentation;
- d) The lot numbering system for intermediates and final products;

A copy of the complete master formula (blank batch record) for one batch size would be desirable. However, the information described below regarding master formulae is preferred.

Note: For combination vaccines, it is suggested to provide the information for each antigen bulk separately (separate chapters such as 5.1A, 5.1B, 5.1C for the antigen bulk production) and with a separate chapter for formulation and filling/lyophilization following (eg 5.1D). If components of the combined vaccine are filled separately and mixed at the time of administration, each final container component would be presented as above and then followed by an additional chapter(eg 5.1E) of information on the final mixed vaccine.

In the case where an updated PSF for other vaccines containing one or more of the same bulk antigens (produced identically by the same manufacturer) is already on file and accepted at WHO, the chapters relative to those bulks can be cross-referenced and not repeated in the PSF for the combined vaccine.

* WHO recommended requirements or guidelines and UN agency tender specifications must be met. For each specific test done, the international standard met should be identified.

WHO, EU and PIC GMP guidelines specify that a Master Formula (MF) be prepared for each batch size of product that is manufactured. A "batch" is by definition *"A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous."* (WHO TRS 908, Annex 4).

The MFs are essentially blank batch records. MFs would be prepared for batches of intermediates, batches of final formulated bulks, and for final product filled/lyophilized lots. For most intermediates, a "batch" is either a quantity of product that must be QC tested and released before further processing and/or that is stored for significant periods and therefore must have stability data and a defined expiry date for use in further processing.

Manufacturers may produce intermediates in several specific batch sizes, and then may formulate and/or fill sizes for a range of volumes depending on customer orders. In these cases, a MF for bulks should be specific for each batch size. For MFs for formulation or filling, these should show the range of volumes handled and must be supported by validation of consistency of the process and the product at both extremes of the production volumes. Stability should be similarly validated.

The complete Master Formula for a vaccine would include the Master Formula of each intermediate/component that is incorporated into the final product.

WHO requests some basic information on the production at various stages to give a clear indication of the production processes.

- a) Fermentation or culture harvest sizes (for each antigen if a combined vaccine).
- b) The amounts (volumes or weights as appropriate) of each ingredient added during formulation for each final formulated bulk batch size (or a list of the range of amounts).
- c) The typical number (or range) of vials and/or number of doses for each fill size (and also lyophilization batch, if appropriate).
- d) How the lot numbering system is designed and how it distinguishes between the various stages of bulk manufacture, filling and lyophilization, and whether the lot numbers indicate sequential lots, include a product code, or include the date of manufacture.

WHO has indicated that a blank copy of the MF would be useful for the review process. As this can often be a very large document and can be reviewed during the site visit, WHO would request at this stage to receive a list of the documents included in the MF (manufacturing instructions, SOPs and records of autoclaving, sterilization, cleaning records, etc) that make up the full batch record for the vaccine under review.

5.2 Description of the manufacturing processes (from master cell bank and virus seeds as applicable) and the characterization of the product together with a detailed flow-chart showing:

- a) Each manufacturing step;
- b) Location (building/room) of each step, and transfers to other building/sites, if applicable;
- c) In-process and quality control tests performed on all intermediates and final products;
- d) Identification of any processes or tests performed by contract manufacturers or testers;
- e) Storage times and temperatures of intermediates.

Details of culture media used, seed expansion procedures, technology (fermentation, cell factories, static or agitated culture) incubation temperature and incubation periods, critical parameters monitored during the culture steps, purification methods used, etc should be provided. For viral vaccines, details of level of cell passaging, multiplicity of infection, etc should be provided.

For recombinant vaccines, a description of the construction and characterization of the recombinant vector as well as source of master cell bank/constructs shall be provided. Include details of the manufacture and QC of any adjuvant and diluents.

The flowchart and accompanying text should provide a clear picture of the full manufacturing and control processes and how the product moves through the cleanrooms and facilities on-site and off-site, as applicable.

The full process for bacterial vaccines will include the strain of bacteria, lot number of the MCB, WCB and storage locations and then follow the charging in of the WCB vials to begin the initial expansion of the cells and continue to the harvesting, DSP as applicable, and finishing (formulation/filling/lyophilization).

For viral vaccines the initial steps will include both the cell or animal host, infection, control cells, growth and harvesting, DSP as applicable, and finishing.

For recombinant vaccines the additional information for the construction and characterization of the recombinant host cell is required.

For combination vaccines, it is suggested to provide the information for each antigen bulk separately (separate chapters such as 5A, 5B, 5C) and with a separate chapter for formulation and filling/lyophilization flowchart and description following (eg 5D). If components of the combined vaccine are filled separately and mixed at the time of administration, each final container component would be presented as above followed by an additional chapter of information on the final mixed vaccine. For bulk antigen(s) identical to bulk(s) in other currently prequalified vaccines by the manufacturer, cross-reference can be made to the other PSF(s) for the bulks (see also Note in 5.1, above)

5.3 Description of general policy for process validation. List of the process validation activities performed.

Provide the reference to the documents describing the policy for process validation (e.g. a section of the Master Validation Plan); a list of the processes validated (e.g. production process(es), cleaning process(es), sterilization/depyrogenation processes, and simulations such as fermentation, lyophilization and media fills); a brief description of each of the validation studies including the selection of worst case situations to cover all situations, the current status of validation, and the re-validation frequency. This could be provided in a table.

For media fills, give the frequency of media fills, media used, incubation conditions, the fill sizes/volumes/# vials/shift simulation, the number of times per year for each of the filling staff, and number of runs.

5.4 Arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage.

Incoming starting materials for production of the vaccine (biological materials such as cells, viruses, active raw materials) as well as packaging materials including Vaccine Vial Monitors, intermediates, and final product. For each of these describe the quarantine labeling and storage, sampling methods and amounts, procedures for moving to released storage for further processing or for distribution.

5.5 Arrangements for the handling of rejected materials and products, and procedures for their destruction.

Describe the process for handling and destruction of raw materials, intermediates, final product found not acceptable by QC or QA, and for any recalled or returned product. Describe the destruction procedures and records taken and archived to demonstrate the fact that they have been destroyed. Indicate any contract company hired to perform the destruction.

Chapter 6: Quality Control*

6.1 Starting materials.

Note: these are raw materials for production.

6.1.1 Control tests performed on raw materials, with appropriate characterization:

- a) List of raw materials meeting compendia specifications, indicating the pharmacopoeia;
- b) List of raw materials meeting in-house specifications including the tests performed and specifications;
- c) List of biological starting materials (human or animal origin) with information on the provisions to avoid risk of Transmissible Spongiform Encephalopathies (TSEs) and human diseases (HIV, hepatitis, etc) in the final product;
- d) List of media with ingredients, tests performed and specifications.

a), b), d) Tables of the requested information with identification of the tests repeated by QC for each raw material (RM), including all formulation excipients and adjuvants, are sufficient. A list of SOP titles and numbers for the raw materials would be useful. For a combined vaccine with several antigens produced, the tables should specify the product for which the RM is used, or else separate tables can be presented for each bulk antigen.

Give the in-house expiry date or retest policy for raw material chemicals.

- c) Biological starting materials should be listed with tests and specifications by the supplier and repeated by QC. Certificates for bovine and human derived products used in production indicating the supplier, source, supplier tests for risk contaminants and results should be provided.

6.1.2 Control tests performed on labelling and packaging material(s), including primary and secondary packaging material.

Give a description of the QC tests and specifications for primary (glass vials, stoppers, caps) and secondary packaging material (boxes) from each supplier.

Give a description of the QC checks, tests and approvals regarding pre-printed materials: colours, content, etc, on each lot from each supplier of pre-printed vial labels/boxes/cartons, leaflets, shipping labels, and any other vaccine-specific printed material.

Describe the QC procedure for issuing of labels, boxes/cartons for the labeling/packaging operations.

If labels and boxes/cartons are printed on-line with computer generated print templates, provide a description of the QC or QA controls for each template and the checks made before releasing templates for labeling of vials, or packaging of labeled product.

Describe the reconciliation of vials, stoppers, caps, labels and boxes/cartons issued/printed, labels and boxes/cartons destroyed during labeling, left-over labels, or labels/boxes taken as samples.

For package inserts (leaflets), describe the controls ensuring the correct leaflet is packaged with the product.

6.1.3 Qualification criteria for suppliers of raw material and relevant certificates.

Describe the procedure for auditing and approving the suppliers of raw materials for production. Describe the documentation reviewed for this purpose and the certificates of analysis required with each shipment of RM.

6.2 Intermediate products (as appropriate).

If the product is a combined vaccine, subchapter 6.2 can be repeated for each antigen (eg 6.2A, 6.2B, etc). If an updated PSF for a currently prequalified vaccine containing any of these antigens is available at WHO that provides such information, then cross-reference to the QA information can be made. If adjuvant is used and manufactured in-house, a separate section (eg 6.2X) should be included.

Note: these are production intermediates that require QC testing and release before use in subsequent manufacturing steps, or bulks for shipment to fillers of prequalified vaccines, where applicable.

6.2.1 List of routine tests performed and specifications for intermediates. Include copies of Standard Operational Procedures (SOPs) for critical QC tests (uncontrolled copies or concise description of the method and retest criteria are acceptable).

Provide a list of the SOP titles and numbers, edition, and revision date of assays performed on each intermediate for the vaccine under review and for final bulk of this vaccine for export, if applicable.

Copies of the critical SOPs or concise summaries are requested.

6.2.2 List of assays validation activities performed.

Provide a list of the assays and the parameters evaluated for the validation of each assay on intermediates or final bulks. The list should also include the current status of the assay validation, the current qualification status of the equipment used in the assay, and the policy for training and evaluation of new lab techs on release assays. A table of the information is acceptable.

6.3 Finished products.

If the product is a combined vaccine with two separate final containers of vaccine components, subchapter 6.3 should be repeated for each antigen (eg 6.3A, 6.3B, etc), followed by a section 6.3X for the tests performed on final mixed vaccine.

- 6.3.1 List of routine tests performed and specifications for final product. Include copies of the SOPs for critical QC tests (uncontrolled copies or concise description of the method and retest criteria are acceptable).

Provide a list of the SOP titles and numbers, edition, revision date, for final vaccine, diluent, and separate vials of vaccine components for combined vaccines, if applicable, for the vaccine under review.

Copies of the critical SOPs or concise summaries are requested.

If any assays are identical to those for intermediates, these can be cross-referenced to section 6.2.1.

- 6.3.2 List of assays validation activities performed.

List the assays and the parameters evaluated for the validation of each assay on final container vaccine(s) and diluent, if applicable. The list should also include the current status of the assay validation, the current qualification status of the equipment used in the assay, and the policy for training and evaluation of new lab techs on release assays. A table of the information is acceptable.

If any assays are identical to those for intermediate, these can be cross-referenced to section 6.2.2.

- 6.3.3 List of final lots internally rejected in the previous two years and reasons for rejection.

A table of: the vaccine and/or diluent, and/or separately vialled vaccine components, as applicable; lot number(s); date of manufacture; reasons for rejection (e.g. production deviation, EM deviation, out of specification test result) with specific failure identified, responsible department deciding the rejection should be provided for the current year to date and the past 2 years.

Chapter 7: Stability

7.1 Stability tests on intermediates:

- a) Assigned shelf life and storage conditions;
- b) QC methods and specifications and rationale for the choice of tests for determining stability;
- c) Identification of the dates of manufacture of the lots, the lot numbers, the vial and dose size, and the scale of production;

Results of quantitative assays must be expressed as a numerical value with the appropriate limits and not as “pass” or “fail”.

For each intermediate that is stored for significant periods of time (usually >30 days) before subsequent processing steps, formulation or filling, provide the expiry date at the approved storage temperatures. Give the QC tests, SOP number, and specifications that were selected for following stability of each intermediate with justification for the choices. The stability study schedule and frequency of each test should be given.

Provide a list of the intermediate lot numbers on test, batch size, scale of production, storage container and volume, and dates of manufacture. Justification of the choice of these intermediate lots is requested. The stability data should be real-time real condition data.

A table should be prepared for each lot giving the results of tests (numerical values) and specifications with discussion of any out-of-specification result and justification for accepting the result in support of the stability.

Conclusions on stability and the claimed shelf life of intermediates should be stated.

7.2 Stability testing of the finished product:

- a) Assigned shelf life and storage conditions;
- b) QC methods and specifications and rationale for the choice of tests for determining stability;
- c) Identification of the dates of manufacture of the lots, the lot numbers, the vial and dose size, and the scale of production;

Results of quantitative assays must be expressed as a numerical value with the appropriate limits and not as “pass” or “fail”.

For the final vaccine(s) vials, indicate the expiry date at the approved storage temperatures for each. Give the QC tests, SOP number, and specifications that were selected for following stability of each intermediate with justification for the choices. The stability programme and frequency of each test should be given, and, for liquid product, stability should be generated on stoppered vials stored both upright and inverted.

Provide for each presentation (doses/vial), a list of the lots numbers on test, batch size, scale of production, vial size, vial orientation, and dates of manufacture. Justification of the choice of these lots is requested. These lots should be representative of the lots for sale to UN agencies, and the supporting data for stability should be real-time real condition data.

A table should be prepared for each lot giving the results of tests (numerical values) and specifications with discussion of any out-of-specification result and justification for accepting the result in support of the stability.

Tables of accelerated stability data are required to define the VVM category to be used with the specific vaccine (stability data at 2 different temperatures are required and these are usually 2-8°C and 37°C or 45°C), however real time data establishes the expiry dating. Conclusions on stability and the claimed shelf life of the vaccine(s) should be presented.

7.3 Stability testing of diluents and reconstituted vaccine in case of lyophilized vaccines.

For lyophilized vaccines, the stability of the diluent in vials/ampoules should be presented to establish the expiry date. Lot numbers, dates of manufacture, tests, specifications and numerical results should be provided as for vaccine in 7.2 - tables are acceptable.

The stability of the vaccine after reconstitution with the diluent should establish the stability of the vaccine after first entry for at least up to 6 hours after reconstitution. Multiple entry of the vial should be simulated. The same criteria and parameters for stability studies on the final product should be followed (see 7.2).

7.4 Description of the policy for assigning the date of manufacture of each component as well as the final product (e.g. combination vaccine) and diluents, as appropriate.

Provide the procedure for assignment of the expiry date of the vaccine(s), e.g from filling date, formulation date, date of potency test, etc. For a combination vaccine with separate vials components, or for lyophilized vaccine and diluent, that are packaged and shipped together, give the policy for assignment of the expiry date on the separate vial(s) and on the boxes/cartons.

If lyophilized vaccine and diluent or combination components are shipped at different temperatures, or in different shipments, and have different expiry dates, indicate how this is communicated to the purchasers/vaccinators.

Chapter 8: Clinical experience

(Details of this chapter are considered adequately detailed and no additional guidance is given).

Note 1: Clinical studies are expected to have been designed and conducted to meet WHO and international GCP principles. Applicants should consult these three documents:

- *WHO TRS 924 (2004), Annex 1: WHO Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations.*
- *WHO TRS 927 (2005), Annex 1: WHO Guidelines on Non-clinical Evaluation of Vaccines.*
- *WHO TRS 850 (1995) Annex 3: Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products.*

Other guidance documents such as ICH (International Conference on Harmonization) guidelines are also relevant.

Note 2: For vaccines whose license was originally obtained some years ago, it is possible that many or all of the clinical trials may not have been performed or monitored to current international standards. For these vaccines all sections should be completed but additional emphasis should be given to information provided in sections 8.1.1, 8.1.5, 8.2.1 and 8.2.2 in order to sufficiently establish a history of safe and effective use.

Note 3: In some cases, where the information received regarding the sections detailed below is not enough or not clear enough, or requires further scrutiny, WHO may request the applicant to submit the raw data.

8.1 Clinical trials information

8.1.1 Applicant's sponsored clinical trial overview

The sponsor should provide a list of all clinical trials performed in all countries that are relevant to the application for WHO prequalification. These should include all studies sponsored by the applicant both before and at any time after initial licensure, whether or not submitted previously to the NRA(s) where the product is licensed. For each study on the list, the following information is required:

- the type of study
- the rationale for its conduct
- the location(s) of study sites
- the dates of the study
- numbers and ages of subjects
- statement of final conclusions on safety and immunogenicity
- date of protocol approval by NRA, if this was done
- level of compliance with GCP including ethics approvals

All publications and abstract about these trials should accompany the submission in section 8.1.1.

In addition the applicant should list any trials that are known to be currently ongoing with details of the study plan and expected date of results.

8.1.2 Other trials with the applicant's product

In addition, the applicant should make every effort to provide a list of all trials, relevant to the application, that were not sponsored by the applicant but in which the product was evaluated.

This list should be compiled from publications identified using an extensive literature search (details of which should be provided) and, in the case of co-licensure agreements, from any other company that holds a license for or a right to market the same product.

8.1.3 Clinical summary

Provide a detailed summary and interpretation of the safety and efficacy data obtained from the pre-licensure clinical studies and all studies performed in the post-licensure period that support the current prescribing information. The summary should pay particular attention to any data that are relevant to the use of the product worldwide at WHO recommended schedules. In the absence of such data, the summary should provide a pre-clinical and/or clinical justification for the extrapolation of the existing data to the likely circumstances of use after prequalification should the vaccine be pre-qualified. This summary should complement, and not replace, the summary written by an independent clinical expert described in 8.1.5.

8.1.4 Assessment reports (AR)

Whenever possible the applicant should provide the clinical sections of the NRA assessment reports from the country of origin and/or country where initially licensed. Assessment reports for both initial licensure and for any subsequent variations to the license for changes relevant to clinical data are requested.

8.1.5 Clinical expert report

Provide an independent clinical expert report on the clinical studies if justification is being made for submitting clinical data that do not fully meet 8.1.3. That is, if the application for pre-qualification is based on the extrapolation of the existing clinical data to the likely circumstances of use after pre-qualification. Also, wherever the data are old or there is a doubt regarding the ethical or regulatory oversight of the trial, the report should discuss the degree of compliance with WHO GCP recommendations and current guidance regarding pre-clinical and clinical trials with vaccines.

8.1.6 Preclinical studies sponsored by the applicant

Provide a simple list of all pre-clinical studies that were sponsored by the applicant in support of use in clinical trials in humans, or for significant changes to manufacture or use. Include in the list any important conclusions. For preclinical studies performed after initial licensure, indicate the reasons for these studies. Any other particularly relevant reports regarding safety aspects, whether or not generated by the applicant, should be provided.

8.2 Documentation of safety

Safety data should be submitted both in the case of the initial application for prequalification evaluation and for reassessment purposes.

8.2.1 Initial evaluation of vaccines that have been in the market for a long time or reassessment of already prequalified vaccines.

- Provide an outline of the applicant's procedures for the collection, onward notification and assessment of Adverse Events.
- Provide a listing of all reported AEFIs for the vaccine in question in the last five years or since the last WHO reassessment. As far as is possible from the reports received, applicants should list the type of reaction, lot number, date and place of immunization, patients initials and age and, for immunization series, the dose number. A judgment of serious/non-serious and whether or not the event was expected (in the light of the prescribing information) should be provided where this was possible from the information. An assessment of the relationship to the vaccine made by a clinician and, where relevant, by the applicant company, or its independent clinical expert, should be included.
- In cases, where ICH- PSURs are available, these can be submitted. Information regarding other geographical areas shall be added to that provided in the PSURs.

8.2.2 Recently licensed vaccines

In the case of vaccines that have been recently licensed, provide information on any ongoing Phase IV studies or on any active monitoring of the safety profile that is taking place.

8.2.3 Documentation of Serious Adverse Events

For Serious Adverse Events reported in the last five years, or as long as the vaccine has been marketed (when shorter than five years), provide full description of each case as possible, including any information there may be on investigations, actions, patient treatment and outcome.

Chapter 9: Production and distribution data

- 9.1 The quantity of finished product distributed domestically and exported in the previous three years. List the different presentations separately, and indicate whether the list gives the numbers of vials or the numbers of doses distributed.

List the number of vials and doses of finished vaccine distributed domestically and internationally for the current year to date and for the past 3 years. A separate list for each presentation should be made (single dose, various multi-doses) and the destination and the purchaser (domestic purchasers, country, UN agencies, etc) is requested.

- 9.2 List of countries where the product is licensed (marketing authorization) and supplied.

Give a list of the countries where the vaccine is licensed (NRA review and approval of a dossier), is registered (on an official list of vaccines in the country), or distributed.

- 9.3 Arrangements and recording system for distribution, including the release process performed by the manufacturer and the NRA.

Give a brief description of the sequential activities and procedures for final product QC testing, internal QA release, NCL release, and the method for shipment describing the details maintained on purchasers, dates of shipments. Indicate whether final filling/packaging is performed based on purchase orders or whether purchase orders are responded to with product already filled/packaged.

- 9.4 Summarize the packaging procedures for international shipments (including box sizes, packing volumes, etc.). Provide the validation protocols and reports of the shipping boxes used for UN supply. Recommendations provided in the most recent version of the WHO “Guidelines on the international packaging and shipping of vaccines” shall be followed.

Describe the boxes used identifying the type/brand and size, the ice/cold packs used and their preparation temperature, the packing volumes, typical vaccine amounts/box size, temperatures to be maintained during shipping for the vaccine(s) under review, and the type of temperature/freeze monitors used. Describe in detail the validation protocol and results for each size shipping container for each shipment. The protocol and report for the validation of the worst case shipment (e.g. greatest distance/time, highest number of package transfers, highest local temperature conditions at destination) is requested. The validation protocol should comply with the most recent version of the WHO Shipping Guidelines (WHO/IVB/05.23)

- 9.5 Describe the arrangements for the handling of complaints and product recalls. Description of the recall investigation system and procedures for corrective actions. Description of regulatory requirements in case of recalls.

Identify the department responsible for handling incoming complaints, investigations and communications regarding such complaints. Describe the procedure to identify if the complaint is potentially related to product quality and the investigation procedure followed to determine this. If a product recall is required, describe the procedure to be followed, the communications required, and identify the agencies/programmes to be notified and the timing of this notification.

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- 9.6 List the quantity of finished product supplied to UN agencies on a per annum basis. List the different presentations separately and indicate whether the list gives the number of vials or the number of doses distributed.

List the number of vials and doses of finished vaccine shipped through UN agencies for the current year to date and for the past 3 years. A separate list for each presentation is requested. The destination and the purchasing agency (PAHO, UNICEF, etc) would be useful.

- 9.7 The quantity of bulk vaccine destined for UN agencies, supplied to contract fillers/packagegers for finalization (list individually).

A list of the amounts and composition, titer, and # doses of bulk vaccine(s) or antigen(s) sent for the current year and the last 3 years for each contract filler is requested.

Chapter 10: Update of Regulatory Authority Actions Relevant to the Product

10.1 Copy of regulatory documentations:

- a) Marketing Authorizations for all formulations,
- b) Information on refusals, withdrawals, or suspensions including those that are manufacturer initiated, both safety and non safety concerns should be identified
- c) GMP certificate or equivalent,
- d) The manufacturer may wish to provide reports of inspections from National or other Regulatory Authorities including any follow up actions may be useful to WHO in that upon review may allow for streamlining the site visit accordingly.

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| <ol style="list-style-type: none">a) Photocopy of the most recent MA, license, or registration for each dose size/volume and/or formulation if excipients differ in the different presentations. The date of issue and the expiry date should be clearly shown or listed separately. If the vaccine and the manufacturing establishment are licensed separately, give a copy of both documents. If a diluent is used, supply the license(s) for it as well.b) Prepare a tabulated list showing the refusals/withdrawals/suspensions domestically and in any country where the product is licensed, registered or distributed. Give the initiator of each action, the reason, and the dates, and also the final outcome and date.c) Provide a copy of the current GMP certificate or document/letter from the national responsible authority confirming compliance with GMP. Give the date of issue and the date of expiry of this GMP certificate/equivalent. If the GMP certificate/letter for the diluent is a separate document include this as well.d) The inspections reports by the NRA are confidential documents that cannot be released without permission of the manufacturer. If this optional request is accepted, the manufacturer should send WHO the reports. Or, if agreed in advance with the NRA, an official letter from the manufacturer permitting the country NRA to release such information may be provided to WHO by the manufacturer with the application for pre-qualification.

The reports, to be useful to WHO, must be complete reports of the observations, the comments and questions to be answered by the company, the action plan and deadlines, and the final opinion of the NRA. |
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10.2 List of lots rejected by the NRA, if applicable.

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| <p>Either "none" or list all restrictions that have been placed on distribution of the product giving the lot numbers, presentation, reason for rejection, the date of manufacture, and the % of lots rejected/year for each presentation (or ratio of lots rejected/total lots produced).</p> <p>If diluent is used, provide the same information for any rejections of lots.</p> |
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10.3 Restrictions on distribution or recalls, including manufacturer-initiated recalls.

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| <ol style="list-style-type: none">a) Either "none" or list all restrictions that have been placed on distribution of the product giving the lot numbers, presentation, reason for restriction, initiator of the restriction, the date of manufacture, the duration of the restriction, the investigation and investigators, and the final outcome (lots rejected, recalled, or re-released). If diluent is used, provide the same information for any restrictions.b) Either "none" or list all recalls of the product with dates, purchaser, lot number, reason for recall, initiator of the recall, and outcome (e.g. time for recall, % of product returned or destroyed, amount of product not accounted for). If diluent is used, provide the same information for any recalls. |
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10.4 Clinical trial suspensions, including manufacturer-initiated suspensions.

Either "none" or list or explain: the trial phase; study title, number and objectives; location of trial; initiator of the suspension, dates of suspension, reason for the suspension, final outcome (trial reinstated and completed, or ended), and dates of trial reinstatement, trial stoppage, or trial completion.

10.5 Dosage or schedule modifications.

Either "none" or explain any changes or modifications to the dose or dose regimen since the license was granted. List the original licensed dose/schedule, the new dose/schedule, and the reasons for the change(s). Give a brief summary of the supporting data and the information submitted to the NRA for approval of the change(s), and the dates of notification and NRA approval.

Describe the regulatory process followed to approve the change(s) (e.g. notifications to the NRA, application and approvals of variations to the license). If clinical studies were performed to support the changes, list here and refer to information in the relevant section of chapter 8, above.

10.6 Changes in target populations or indications.

Either "none" or explain any changes in target population (e.g. ages, sub-populations or vulnerable populations added or eliminated) and/or changes in indications since the license was granted. List the original licensed target populations/indications, the new target populations/indications, the reasons for the change(s), a brief summary of the supporting data, the information submitted to the NRA for approval of the change(s), and the dates.

Describe the regulatory process followed to approve these change(s) (e.g. notifications to the NRA, application and approvals of variations to the license). If clinical studies were performed to support the changes, list here and refer to information in the relevant section of chapter 8, above.

10.7 List of inspections conducted by National Regulatory Authorities within the previous two years, including the scope of each inspection.

Provide a list of the dates of inspections, the national and/or state inspection authority(ies) performing the inspection, the inspector(s), and the scope (initial, routine, special, focused, follow-up, etc) and the product(s), areas, facilities, departments, or activities inspected.

10.8 List of inspections conducted by foreign authorities within the previous two years, including the scope of each inspection.

Provide a list of the dates of inspections, the name of the country and the country inspection authority(ies) performing the inspection, the inspector(s), and the scope (initial, routine, special, focused, follow-up, etc) and the product(s), areas, facilities, departments, or activities inspected.