GUIDELINE ON CTD DOSSIER EVALUATION OF VACCINES IN BANGLADESH

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MESSAGE FROM THE DIRECTOR GENERAL

It is my pleasure that one of the nine functions of DGDA – "Marketing Authorization" related guidelines are now regularly published from DGDA for different classes of drugs. On this aspect "GUIDELINE ON CTD DOSSIER EVALUATION OF VACCINES IN BANGLADESH" is one of the very important guidelines which will help Vaccine Manufacturers, Researchers, Academicians as well as Regulators to ensure quality, efficacy and safety of Vaccines registered in Bangladesh. This guideline is prepared harmonizing with ICH M4: The Common Technical Document Guideline. So that Vaccines registration would be given in Bangladesh with a high standard to get global recognition as well as protecting the health of the patients who are in dire need of these products. I would like to thank the members of working committee for their meticulous job which they performed.

13.07.23

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Director General
Directorate General of Drug Administration
& Licensing Authority of Drugs

Members of "Guideline on CTD Dossier Evaluation of Vaccines in Bangladesh"

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Table of Contents

LIST OF ABBREVIATIONS

ACTD	ASEAN Common Technical Document(s)
ADR	Adverse Drug Reaction
AR	Assessment Report
ASEAN	Association of South East Asian Nations
B.E.	Before Era
BP	British Pharmacopoeia
B/R	Benefit/Risk
CTD	Common Technical Document(s)
DNA	Deoxyribonucleic acid
ERA	Environmental Risk Assessment
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMOs	Genetically Modified Organisms
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization
ICHCTD	ICH Common Technical Document(s)
IND	Investigational New Drug
IP	International Pharmacopoeia
MA	Marketing Authorization
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
NCL	National Control Laboratory
NF	National Formulary
NRAs	National Regulatory Authorities
PAR	Public Assessment Report
Ph Eur	European Pharmacopoeia
PL	Package Leaflet
QOS	Quality Overall Summary
SOP	Standard Operating Procedure
SMPC	Summary of Product Characteristics
DGDA	Directorate General of Drug Administration
USP	United States Pharmacopoeia
WHO	World Health Organization

1. INTRODUCTION

Responsibility for the quality, safety and efficacy of vaccines lies first and foremost with the manufacturer/marketing authorization holder (MAH). The Directorate General of Drug Administration (DGDA), Bangladesh must establish procedures to ensure that the products and manufacturers meet the established regulatory criteria.

Vaccines are products of biological origin which exhibit some intrinsic variability. They are characterized by complex manufacturing processes and are administered to large numbers of healthy children, adolescents and adults. Their quality cannot be assessed solely by testing the final product alone. It is recommended that the DGDA establishes a specific regulatory system for this type of product.

A basic function of DGDA is to evaluate the quality, safety and efficacy of vaccines. This involves authorizing their use, distribution and sale, which implies granting a market authorization (MA) and keep vaccines and biosimilars in post market surveillance. In order to license a vaccine, the DGDA has set requirements for applicants to comply with. These requirements include the information needed in the application dossier and evidence that the vaccine has passed the stages of research, development, production and quality control, as well as clinical testing, and that the quality, safety and efficacy required of the vaccine to be used in humans has been established. Another important aspect to consider in the vaccine evaluation process is that the manufacturing facilities must comply with good manufacturing practices (GMP). Therefore, DGDA staff as well as External Experts must be trained and have the experience needed to do the evaluation.

2. LEGAL BASIS

Drug control ordinance 1982 & Drug act 1940 clearly defines that no drug can be manufactured in or imported into Bangladesh unless it obtains a marketing authorization from DGDA, Bangladesh.

Drug act 1940 & Drug control ordinance 1982 identify the following:

The whole application dossier consisting of quality, non-clinical and clinical information according to the Common Technical Documents (CTD) for marketing authorization shall be accompanied with the following particulars:

- Trade name
- Formulation
- Pack size
- Analytical method
- Label
- Product leaflet

- Other document as listed in the checklist.

Variation of any marketing authorization cannot be proceeded unless it obtains prior approval from DGDA mechanism to handle the application for marketing authorization and the application for variation as well as the issuing of the Annexure Approval of Drug Registration or variation should be in accordance with Drug act 1940 clearly defines the duties of the Drug Committee to give advice or justification of drugs to be manufactured, sold or imported into Bangladesh and its Marketing Authorization.

3. SCOPE

This guideline applies to all vaccines to be licensed by DGDA for use in humans. The guidance provided in it shall serve as the administrative and scientific basis for the assessment of vaccines by both DGDA Team, Staff of Biological Products Section and External Experts appointed by the DGDA.

Vaccine Definition:

'A vaccine is an immunogen, the administration of which is intended to stimulate immune system to result in the prevention, amelioration or therapy of any disease or infection. A vaccine may be a live attenuated preparation of bacteria, viruses or parasites, inactivated (killed) whole organisms, living irradiated cells, crude fractions or purified immunogens, including those derived from recombinant DNA in a host cell, conjugates formed by covalent linkage of components, synthetic antigens, polynucleotides (such as the plasmid DNA vaccines), living vectored cells expressing specific heterologous immunogens, or cells pulsed with immunogen. It may also be a combination of vaccines listed above'.

Biologics definition:

Biologics are biological products derived from living cells/ organisms.

Biosimilars:

Biosimilars are biologics which are introduced after expiration of patent / exclusive marketing rights. These are similar to the originator products. Biosimilars are follow-on biologics.

The assessment of the information and data submitted by an applicant for a marketing authorization of vaccines and biologics occurs in three stages:

The first stage is the administrative handling of the incoming documents and initial review / validation of the submitted documents to make sure that all the required information has been provided according to the *'Guideline for Production and Quality control of Vaccines in Bangladesh' also 'DGDA Registration Guidelines of Biosimilars 2018'*, available to the

applicant.

The second stage is the assignment of the various parts of the dossier to be evaluated by CMC and clinical trial members of MA and CT Team. In case of unintroduced vaccines, first those are sent for evaluation and opinion from experts of CMC expert committee as well as toxicology and clinical trial expert committee. Having favorable opinion, those are placed to working DCC technical committee and DCC for primary registration (recipe) approval.
In the third stage: DGDA CMC team/ member review CMC data and laboratory experts go through test analysis reports and related test reports, test method validation protocol and record also they analyze / test submitted batch(s) of the vaccine. If there is no deficiency found during the evaluation / review, review report / file submitted to deputy director. Deputy director places files to Director (Head of MA). Head of MA goes through all review reports and develop / compile evaluation final report approving / disapproving registration to licensing authority (DG). Licensing authority authorizes approval / disapproval. If any deficiency found, place it to head of MA, if he finds a major / critical deviation / deficiency then he places it to licensing authority for issuing a deficiency / deviation letter.
For introduced vaccines and biologics, documents are directly evaluated by the MA CMC, CT and lab experts as mentioned before.
The procedures described in this guideline will include consistently applied administrative handling of incoming applications and documents, proper tracking and filing, and maintaining confidentiality of the information received.
The procedures described in this guideline can serve as a basis for assessment reports of all stages of a primary application procedure until a licensing decision is made as well as for variations to the marketing authorization for authorized vaccines.

4. PURPOSE OF THE ASSESSMENT CHECKLIST REPORT (AR)

The assessment checklist report (AR) is the key document explaining why a marketing authorization and each of the proposed indications have been or can be approved or rejected by the DGDA. The AR also serves as an audit trail explaining why an authorization has been proposed as, granted, or rejected and explaining the terms of the Summary of Product Characteristics (SMPC), Package Leaflet (PL) and Label(s). The report should be sufficiently detailed to allow for secondary assessment by other NRAs experts. For reasons of transparency part of this assessment report of non-commercial and non-confidential information should be used and made publicly available as a Summary Technical Evaluation Report.

An explanation of and justification for each part of the SMPC, PL and Label(s) should be made referring to the relevant supporting data in the dossier. Where it is recommended that a marketing authorization to be granted is subject to conditions, these should be set out, clearly indicating the rationale and the timetable for receipt of results necessary to fulfil the additional requirements.

The assessment will be performed according to Pharmacopoeia Monographs such as BP, USP/NF and Ph Eur which are legally binding; in absence of these, or otherwise justified, WHO and other relevant International Guidelines apply. Deviation from WHO and other relevant International Guidelines needs to be justified by the applicant and the justification be assessed by the DGDA.

5. RECOMMENDATION (regarding the licensing decision taken by DGDA)

Based on the review of the data on quality, non-clinical safety and clinical safety and efficacy the DGDA considers that the application for the vaccine <product name>, in the prevention and / or treatment of <claimed indication>, <is not approvable since 'deficiencies' have been identified, which preclude a recommendation for marketing authorization at date and time>, <is approvable or not approvable based on the additional information provided by the applicant> State the need for an inspection (GMP, GLP and/or GCP).

6. QUALITY ASSURANCE

The AR ought to be subject to a quality assurance program within the DGDA.

7. CONTENTS OF THE ASSESSMENT CHECKLIST REPORT

In general, the assessment report should consist of four parts:

- Overview (shall consist of Overall Summaries on Quality, Non-Clinical and Clinical Aspects)
- Quality Data
- Non-Clinical Data
- Clinical Data

7.1 Overview (proposed by DGDA) should include the following information:

7.1.1 Executive Summary

7.1.1.1 General Guidance

The Executive Summary should deal with all Quality, Non-Clinical and Clinical aspects.

For each main section of the assessment report for Non-Clinical and Clinical documents, the report should describe the data submitted. For each type of study, after distinguishing between main and supportive data, it should be assessed whether the

main data consist of all the particulars and documents of Non-Clinical or Clinical study reports ('original data'), bibliographical references, a combination of the two, or if data are absent. The data submitted should be assessed based on the legal basis of the application, other legal / regulatory data requirements, applicable guidelines and other scientific criteria.

The types of studies addressed within each section should include all references in accordance with relevant International Guidelines.

When available data deviate from legislative requirements and guidelines: Where the data submitted deviate from the requirements, the acceptability of any justifications should be assessed. In particular, absence of any data for Non-Clinical / Clinical test or trials, or use of bibliographical references substituting in part or completely original data for main studies must be justified.

Examples of justifications and assessment of the justifications are provided in the following table:

Justification	Assessment
- Specific derogations from relevant International Guidelines.	- Mention specific derogations and confirm the reasons why the application fulfils the conditions for applying them.
- Due to the extent of scientific knowledge the conduct of certain clinical trials is considered unethical or the conduct of certain animal tests is considered to lead to unnecessary use of animals (for instance, due to extensive clinical experience certain toxicological tests are considered unnecessary)	- Discuss what evidence is the basis for the scientific knowledge, the relevance and reliability of such evidence and assess the validity of any extrapolation. Given that evidence, assess whether repeating certain trials / tests (or conducting additional tests) would extend scientific knowledge essential for benefit-risk assessment and provision of adequate information to patients and prescribers.

7.1.1.2 Problem Statement

The AR describes the rationale for use of the vaccine in Bangladesh, the main features of the diseases the vaccine is directed against, and/or the currently in Bangladesh available comparable vaccines, unless justified.

7.1.1.3 About the Product

The AR identifies vaccine classification, claimed indication, posology and

recommendation for use.

7.1.1.4 The Development Program/Compliance with Relevant International Guidelines and DGDA Scientific Advice

Introduce and comment the clinical development program during the IND Phase in view of the proposed indication and posology.

State if, and when scientific advice has been given, describe the issues and indicate whether the advice was followed by the applicant. Indicate if the applicant followed relevant International Guidelines and if any deviations have been adequately justified.

Indicate availability and need for pediatric development and development in other special populations such as the elderly, male/female and ethnic minorities. State the number and characteristics of healthy volunteers/patients/males/females included in the studies, as appropriate.

7.1.1.5 General Comments on Compliance with GMP, GLP and/or GCP

Elaborate as appropriate in concordance with points made in the assessment reports. A specific comment should be made as to whether any inspections are needed and if so whether it is GMP, GLP and/or GCP.

Where it is considered that one or more inspections are required make a cross reference to the detail in sections on GMP, GLP, or GCP in the related Quality, Non-Clinical, or Clinical reports. The inspection request should be referenced in the relevant part of this document.

7.1.1.6 Type of Application and other Comments on the Submitted Dossier

Indicate type of marketing authorization application (reference to the legal basis of the application), for example:

Indicate if acceptable justifications exist for waiving certain studies or replacing original studies by literature data. If certain studies are only available as publications it is important to clarify whether or not such studies are/are not of sufficient quality to allow an in-depth assessment of crucial data.

Indicate if the applicant has requested *accelerated assessment* and the fulfilment of relevant criteria.

Indicate if the applicant has requested a *routine marketing authorization or an approval under EUA circumstances*. The assessment of the fulfilment of relevant criteria is an integrated part of this report (for further guidance, please see relevant

DGDA Regulation).

For *routine approval*, the DGDA team should assess the validity of the reason(s) put forward by the applicant. In brief address the following: serious/life threatening disease; emergency threat; positive Benefit/Risk (B/R); medical need; does immediate availability outweighs the risks? For conditional approval the positive B/R is made pending results of further studies. Discuss those studies in terms of feasibility once the product is on the market.

For *EUA circumstances*, the DGDA team should assess the validity of the reason(s), In brief: address particularly the items relevant to rarity, ethics or stage of scientific knowledge and the type of specific obligations that may be necessary. For an approval under exceptional circumstances, it is in principle not foreseen that the applicant can provide comprehensive data on efficacy and safety.

7.1.2 Scientific Overview and Discussion

7.1.2.1 *Introduction*

Although this assessment report shall include the necessary details to understand what is in the dossier, DGDA team and the External Experts are requested to focus on the salient findings from each part of the assessments on Quality, Non-Clinical, Clinical and Pharmacovigilance, with a discussion / interpretation of the results giving the grounds for the benefit-risk assessment and the DGDA recommendations and the questions posed to the applicant.

7.1.2.2 Quality Aspects of Drug Substance(s) (DS) and Drug Product (DP)

The quality overview reviews the information related to the chemical, pharmaceutical and biological data of the vaccine. Key critical parameters and issues related to quality aspects shall be emphasized, including adherence to relevant Pharmacopoeia Monographs and other relevant International Guidelines. Any novel adjuvant(s) and preservative(s) shall be subject to a specific quality assessment.

7.1.2.3 Non-Clinical Aspects (Pharmacology, Pharmacokinetics and Toxicology)

The non-clinical overview reviews the non-clinical evaluation of the vaccine in animals and in ,vitro, including adherence to relevant equivalent International Guidelines. Comparability of product used in non-clinical studies, clinical studies and vaccine for marketing shall be assessed. Any novel adjuvant(s) and preservative(s) shall be subject to a specific safety assessment.

7.1.2.4 Clinical Aspects (Pharmacodynamics, Clinical efficacy, Immunogenicity, Safety and Pharmacovigilance plan)

The clinical overview provides a critical analysis of the clinical data, including

adherence to relevant equivalent International Guidelines. The clinical overview reviews also the assessment of the way how the efficacy and safety findings support the vaccine dose, target indications, and particulars of the summary of product characteristics (SMPC).

The clinical overview considers also whether the pharmacovigilance plan proposed by applicant is adequate. Deficiencies should be described and implemented before vaccine is put onto the market.

7.2 Assessment of Quality Data

7.2.1 Advice to DGDA team on Quality Assessment

The following general aspects should be considered:

Cross-references should be used to clearly indicate the origin of any information used in the report, such as the specific parts of the dossier (e.g. overview, summary, study reports), references to the literature or other sources.

The Quality assessment report should also emphasize those findings that need to be reflected in the SMPC.

Where the data submitted deviate from the requirements, the acceptability of any justifications should be assessed.

For each main section of the Quality assessment report should describe the data submitted.

This Quality assessment checklist report should be 'self-standing'. This may be achieved in the following way:

1) Presenting comments on data which are taken from the applicant's dossier, followed by DGDA teams assessment of these data, particularly with respect to safety/efficacy consequences and highlighting adherence to specific guidance documents.

The following specific scientific aspects should be considered:

The Quality assessment will be performed according to Pharmacopoeia Monographs such as BP, USP/NF and Ph Eur, which are legally binding; in absence of these or otherwise justified, WHO and other relevant International Guidelines apply. Deviation from WHO and other relevant International Guidelines needs to be justified by the applicant and the justification be assessed by the DGDA.

Quality expert staffs may contribute to the assessment report as follows:

(1) Evaluate general information on quality aspects and information related to the starting and raw materials contained in the marketing authorization application

dossier. This means overall expertise is needed with regards to the following information on the Drug Substance(s) and Drug Product: the manufacturing process, the characterization and properties, the quality control operations and requirements, the stability as well as the description of the composition and presentation of the Drug Product. Starting materials of biological origin for vaccines, such as microorganisms, cells or fluids (including blood or plasma) of animal or human origin or cell substrates as well as raw materials of biological origin require special expertise with regards to their inherent variability and possible contamination with adventitious agents.

(2) Evaluate the manufacturing process and controls of the Drug Substance(s) and Drug Product contained in the marketing authorization application dossier. This means expertise is needed with regards to the following information on the Drug Substance(s) and Drug Product: description of the manufacturing process and process controls in compliance with appropriate information as laid down in Guidelines mentioned above and in-depth knowledge on additional requirements for products of biological origin, for instance vaccine production based on seed lot systems and cell banks or for live vaccines, the stability of the attenuation characteristics.

Furthermore, seed materials, cell banks, pools of serum or plasma and other materials of biological origin shall be used only if the presence of adventitious agents is unlikely or if further processing ensures that their elimination / inactivation can be guaranteed.

(3) Evaluate the quality and the controls of the excipients. This means expertise is needed with regards to the following information on the excipients: materials meet standards appropriate for their intended use, especially with regards to purity, specifications and their justification are presented, analytical procedures are described and duly validated. Once again, specific attention shall be paid to excipients of human or animal origin. The prevention of the transmission of Spongiform Encephalopathies (TSE) via excipients must be demonstrated.

Excipients must comply with current '*WHO Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products*' or other equivalent International Guideline(s). Caution is needed for novel excipients used for the first time in a vaccine. Full details of manufacture, characterization, and controls, with cross-reference to supporting safety data, both non-clinical and clinical, shall be provided and carefully evaluated;

(4) Evaluate proposed quality control methods / specifications and reference standards. This means expertise is needed with regards to the following information: data on the structure of the Drug Substance(s) and Drug Product based on physicochemical, immunochemical and/or biological methods as well as on impurities, information on the specifications used for routine control of the Drug Substance(s) and Drug Product (including release and shelf-life specifications), justification for these specifications, methods of analysis and their validation. The results of controls carried out on three (3) individual batches should be assessed. Reference preparations and standards used for testing shall be identified and described in detail.

(5) Evaluate stability data of Drug Substance(s) and Drug Product and the proposed shelf life. This means expertise is needed with regards to the following information: the types of stability studies conducted, protocols used, detailed results of the studies, including the information on the analytical procedures used to generate the data and validation of these procedures. For vaccines, information on cumulative stability of Drug Substance(s), Intermediates and Drug Product should be assessed, where needed. It is state-of the-art to provide a post authorization stability protocol for evaluation as well as commitments regarding additional stability studies. Stability studies should be performed evaluated in compliance with the relevant WHO Guideline or other equivalent International Guideline(s).
In addition, the AR must give an indication of compliance with (or indicate deviations from) the requirements of GMP.
A standard recommendation sentence with regards to the review of data on quality could read: based on the review of data on quality the experts consider that the application for vaccine <product name> could be approvable provided that satisfactory responses are given to checklist.

If there remain any concerns with respect to quality, it would be helpful if the quality experts indicated whether these might for example be addressed by amending the SmPC.

7.2.2 Information on Quality Data (Chemical, Pharmaceutical and Biological)

7.2.2.1 Contents

Corresponds to the basic principles and requirements of the Drug Substance(s) and Drug Product. Includes the chemical, pharmaceutical, and biological data on development, the manufacturing process, analysis certificates, characterization and properties, quality control, specifications and stability of each of the Drug Substance(s) and Drug Product, as indicated below.

7.2.2.2 Drug Substance(s)

The information requested under this point should be supplied individually for each antigen in the vaccine.

7.2.2.2.1 General Information, Starting Materials and Raw Materials

- Name of the Drug Substance(s) based on the Pharmacopoeia Monographs such as BP, USP/NF, Ph Eur or other relevant International Guidelines such as WHO, as appropriate.
- Structural and molecular formula and relative molecular mass, when applicable, for example in synthetic vaccines containing polysaccharides or proteins. In this case, include the schematic amino acid sequence, indicating the glycosylation sites or other modifications and relative molecular mass.
- Description and characterization of the Drug Substance(s), including physicochemical properties and biological activity.
- General description of the starting materials of biological origin used to obtain or extract the Drug Substance(s). For each biological starting material include a summary of viral safety of the material(s):
  - ✓ Strain: Information on the origin, number of passages, identification, certificates analysis, processes of attenuation, development or construction and genetic stability, depending on the type of vaccine strain.
  - ✓ Master/working seed bank systems: Information on the origin, identification, characterization, preparation method, analysis certificates, determination of foreign agents, stability, controls, and frequency of the tests, definition of the number of passages. In the case of cell banks, demonstrate that the characteristics of the cells remain unaltered in the passages used in production and successively.
  - ✓ Use of fertilized eggs: Information on their origin, identification, quality certificates.

- General description of the raw materials. Considering the raw materials used in the preparation process from which the Drug Substance(s) is not directly derived, such as culture media, bovine fetal serum, etc. Submit information on manufacturer(s), quality certificates, controls performed. In the case of raw materials of animal origin, describe the origin and criteria for selection, shipping, and conservation, and submit a certificate on reduction of the risk of transmission of agents related to animal spongiform encephalopathy.

7.2.2.2.2 Manufacturing Process of the Drug Substance(s)

- Manufacturer(s). Give the name, address and responsibilities of the manufacturer(s).
- Description of the manufacturing process of the Drug Substance(s). Submit a description of the manufacturing process that includes all the stages. A typical production process for a vaccine starts with a vial(s) from the respective seed and / or cell bank, including cell cultures, harvest(s), purification, modification reactions (when applicable), filling, storage, and transfer conditions. Where applicable, include the number of passages.
- Flow chart of the production process, showing all the manufacturing steps, including intermediate processes.
- Description of the lot identification system. Identification of the lot in each stage of the process, including when mixtures are made. Also submit information on the manufacturing scale and lot size.
- Identification of critical steps in the process and controls performed, from the original inoculation until the Drug Substance(s) is obtained, defining the operational parameters or aspects to be controlled during the critical stages, including acceptance criteria.
- Description of the inactivation or detoxification process when applicable. Methods and agents used, parameters controlled, and production stage in which it is performed.
- Description of the purification process. Method used, reagents, and materials used, Operating parameters controlled, and specifications. Conditions for the use and re-use of membranes and chromatography columns and the respective validation studies.

- Description of the process for conjugation and/or modification of the Drug Substance(s), when applicable. Also include information on the origin and quality control of the starting material used to obtain the substance used as protein carrier.
- Stabilization of the Drug Substance(s). Description of the steps performed to stabilize the Drug Substance(s), for example, the addition of stabilizers or other procedures, when applicable.
- Reprocessing. Description of the procedures established for reprocessing the Drug Substance(s) or any intermediate product(s), criteria and justification.
- Procedure for filling the Drug Substance(s), process controls, storage and transport.
- Description of the procedure for packaging the Drug Substance(s), process controls, acceptance criteria, type of container closure system, type of seal on the container used to store the Drug Substance(s), storage and transfer conditions, when applicable.
- Selection and justification of critical stages in the manufacturing process, process controls, and acceptance criteria.
- Validation of the manufacturing process. Information on validation procedures and/or evaluation of the manufacturing procedures, including reprocessing, establishment of critical steps, and criteria for establishing the control limits on the critical steps.
- Description of changes. Describe and justify significant changes in the production process of the Drug Substance(s), during development. State the number of lots prepared during development, production scale, use of each lot, for example stability study, non-clinical or clinical study.

7.2.2.2.3 Characterization of the Drug Substance(s)

Present data to determine the structure and physicochemical, immunological, and biological characteristics of the Drug Substance(s).

7.2.2.2.4 Quality Control of the Drug Substance(s)

- Description of the analytic procedures, validation, and justification of the quality specifications.
- Production consistency. Summarized protocol of the production and control of three (3) consecutive lots of Drug Substance(s), analysis certificates in the event this information is not included in the summarized protocol for the Drug Product, an analysis of the results of these lots in terms of production consistency.

7.2.2.2.5 Reference Standards or Materials

Detailed description of the reference standards or materials used and analysis certificates.

7.2.2.2.6 Packaging and Container Closure System of the Drug Substance(s)

Full description of the packaging and container closure system in which the Drug Substance(s) will be stored until used for preparing the Drug Product. The information should include identification of all the materials that constitute the packaging container closure system and their specifications. When applicable, discuss the types of materials selected with respect to protection of the Drug Substance(s) against humidity and light.

7.2.2.2.7 Stability of the Drug Substance(s)

- Protocol for the stability study, results and conclusions. Should include the Study conditions, including all the storage conditions (temperature, humidity, light) in which the vaccine is evaluated, analytical method, specifications, results, and conclusions.
- Stability program or stability commitment. Refers to the continuation of the stability study, including the number of lots to be included in the study each year and the tests to be performed.
- Storage and transportation conditions for the Drug Substance(s), when applicable.
- Describe the equipment used, areas, and buildings (if pertinent) and the shipping and storage conditions.

7.2.2.3 *Drug Product*

7.2.2.3.1 *Description and Composition of the Drug Product*

This should include a description of the Drug Product, its composition, listing each of the components, Drug Substance(s), adjuvant(s), preservative(s), stabilizer(s), and excipient(s), stating the function of each of them. For lyophilized products, also include a description of the diluent and the container closure system employed for the diluent.

7.2.2.3.2 *Pharmaceutical Development*

Information on the studies performed to establish the dosage form, formulation, manufacturing process, and the container closure system used for final product. The studies described in this point are different from the routine quality control tests performed in accordance with the product specifications. Include the following aspects:

- Drug Substance(s). Compatibility with the rest of the components in the Drug Product, including adjuvant(s), preservative(s), stabilizer(s), as applicable.
- Drug Product. Development of the formulation, considering the proposed route of administration. Physicochemical and biological properties of the product, indicating the relevant parameters for developing the Drug Product.
- Development of the manufacturing process. Description of the selection and optimization of the manufacturing process, particularly for critical aspects.
- Container closure system selected. Information on the materials selected, protection against humidity and light, compatibility of the materials.

7.2.2.3.3 *Manufacturing Process of the Drug Product*

- Manufacturer(s) Give the name, address, and responsibilities of the manufacturer(s) involved, including contract manufacturer(s) for production and quality control.
- Lot formula. Provide the formula of the production lot, including a list of all components.

- Description of the manufacturing process of the Drug Product. Submit a flowchart of the process including all the steps in the process and indicate the points at which the material enters the process, identify the critical steps and control points in the process, intermediate products, and final product. Also include a narrative/description of the manufacturing process, the in-process controls, and the critical points identified.
- Control of critical and intermediate steps. Tests and acceptance criteria developed to identify the critical steps in the manufacturing process and how they were controlled.
- Validation and/or evaluation of the processes. Description, documentation, and results of the studies on validation and/or evaluation of the manufacturing process, including the critical steps or critical tests employed in the manufacturing process. It is also necessary to provide information on the viral safety of the product, when applicable.

7.2.2.3.4 Control of the Adjuvant(s), Preservative(s), Stabilizer(s), and Excipient(s)

- Specifications: Provide information on the specifications for all the substances employed in the formulation of the Drug Product that are different from the Drug Substance(s).
- Analytical procedures. Description or bibliographical reference of the methods used to control these substances.
- Justification of specifications of the substances used in formulating the final product.
- Human or animal substances. Provide information on the source, origin, description of the quality tests performed, specifications, determination of adventitious agents, and viral safety.
- New adjuvant(s), preservative(s), stabilizer(s), and excipient(s). When used for the first time in a vaccine for human use or for a new route of administration, provide all information on the manufacture, characterization, and control, and data supporting safety established in non-clinical and clinical studies in relation to the Drug Substance(s) used.

7.2.2.3.5 Quality Control of the Drug Product

- Specifications. Indicate the specifications for the Drug Product.

- Analytical procedures (summaries or references not accepted). Information on the analytical procedures used for quality control of the Drug Product.
- Validation of the analytical procedures. Information on the validation of the analytical procedures for the Drug Product, including experimental data.
- Lot consistency and analysis. The production and control protocols for at least three (3) lots of Drug Product should be submitted and an analysis of the results for those lots in terms of production consistency.
- Characterization and/or determination of impurities, as applicable, depending on the method used to manufacture the vaccine submitted for marketing authorization.
- Justification of specifications. Provide justification of the specifications proposed for the Drug Product.

7.2.2.3.6 Reference Standards and Materials

Provide information on the reference standards and/or materials used in the tests to control the Drug Product.

7.2.2.3.7 Packaging and Container Closure System of the Drug Product

Describe in detail the type and form of packaging and container closure system of the Drug Product, including the materials of which they are made and quality specifications.

7.2.2.3.8 Stability of the Drug Product

- Protocols and results of the stability study that justify the proposed validity period.
- Submit the stability study that complies with current *WHO Guidelines on Stability Evaluation of Vaccines*' or other equivalent International Guideline(s), including the study protocol, specifications, analytical methods, detailed description of the container closure system for the product evaluated, storage conditions (temperature and relative humidity), in general, results for at least three (3) lots of Drug Product prepared from different or same lot of Drug Substance(s), conclusions, and proposed validity period. The stability studies should be signed by the professional in charge of the study.

It is important to provide additional studies on the stability of the vaccine in intermediate stages in the manufacturing method that require different temperatures from the storage temperature, studies of challenge temperatures, photosensitivity or other specifications, depending on the type of vaccine, evaluated for at least three (3) lots. For lyophilized vaccines demonstrate the compatibility between the lyophilized product and the diluent.

- Post-approval stability program. Include the stability program or stability commitment to be carried out once the vaccine is in the market, including the number of lots to be included in the study each year and the tests to be performed. These results should be submitted periodically to update the information on the stability of the vaccine evaluated.
- Description of the procedures used to guarantee the cold chain. Describe in detail the measures used to guarantee adequate temperature and humidity conditions for shipping the Drug Product from the place of production to the place of final sale, including all the storage and distribution stages and indicating the controls performed in each of the stages. This description should be signed by the professional responsible for it.

The following information may be needed on a case-by-case basis.

(1) Equipment and facilities: production flow chart, including materials, equipment, personnel, waste, and intermediate products in relation to the manufacturing areas; information on adjacent areas related to protection and maintenance of the integrity of the vaccine.

(2) Evaluation of the safety of adventitious agents: Additional, detailed information on evaluation of the safety of the product in relation to adventitious agents of both viral and non-viral origin.

7.3 ASSESSMENT OF NON-CLINICAL DATA

7.3.1 Advice to DGDA team on Non-Clinical Assessment

The following general aspects should be considered:

The Non-Clinical assessment report should be sufficiently detailed to allow for secondary assessment by other experts and DGDA team. The Non-Clinical assessment report should describe salient findings & deficiencies.

Cross-references should be used to clearly indicate the origin of any information used in the report, such as the specific parts of the dossier (e.g. overview, summary, study reports), references to the literature or other sources.

The Non-Clinical assessment report should indicate whether findings have implications for human safety.

The Non-Clinical assessment report should also emphasize findings that need to be reflected in the SmPC.

For each main section of the Non-Clinical assessment report should describe the data submitted.

For each type of study, after distinguishing between main and supportive data, it should be assessed whether the main data consist of all the particulars and documents of non-clinical study reports ('original data'), bibliographical references, a combination of the two, or if data are absent.

Where the data submitted deviate from the requirements, the acceptability of any justifications should be assessed. In particular, absence of any data for non-clinical test or trials, or use of bibliographical references substituting in part or completely original data for main studies must be justified.

The following specific scientific aspects should be considered:

Non-Clinical studies should comply with the *'World Health Organization Guidelines on Non-Clinical Evaluation of Vaccines', WHO Technical Report Series No. 927, 2005*, (most recent version) or other equivalent International Guideline(s). Non-Clinical expert staffs may contribute to the Non-Clinical assessment report as follows:

(1) provide licensing recommendations based on non-clinical safety/protection aspects and provide comments to the Executive Summary prepared by DGDA team describing whether the studies performed comply with the requirements;

(2) provide comments to the scientific overview and discussion on non-clinical safety/protection aspects which summarize the salient results from the main studies, emphasizing those predicting potential adverse events in humans;

(3) provide comments on the relevance of the animal species used in non-clinical testing for human safety assessment;
(4) statements on GLP should also be provided to the AR, and any concerns raised during the assessment should be specifically addressed and the need for a GLP inspection be discussed.
Furthermore, Non-Clinical expert staffs may contribute to the Non-Clinical assessment report as follows:
(5) provide recommendations on conditions for the marketing authorization (e.g. propose specific non-clinical obligations and follow-up measures) and product literature (SMPC, PL) based on non-clinical safety/protection aspects and
(6) the Environmental Risk Assessment (ERA) may be required as part of the Non-Clinical evaluation of possible risks to the environment connected with the release of vaccines containing or consisting of Genetically Modified Organisms (GMOs).
Where the data submitted deviate from the requirements, the acceptability of any justifications should be assessed.
A standard recommendation sentence with regards to the review of data on Non-Clinical aspects could read: based on the review of data on Non-Clinical the expert staff consider that the application for vaccine <product name> could be approvable provided that satisfactory responses are given to checklist.
The Non-Clinical expert staffs should also develop an overview section which is more focused, with discussion indicating any important or interesting issues and any concerns over the Non-Clinical aspects of the product. If there remains any concerns with respect to Non-Clinical aspects, it would be helpful if the Non-Clinical expert staffs indicated whether these might for example be addressed by amending the SmPC.

7.3.2 Information on Non-clinical Data

7.3.2.1 Pharmacology

7.3.2.1.1 Pharmacodynamic Studies (Immunogenicity of the Vaccine)

7.3.2.1.2 Pharmacodynamic Studies of Adjuvant(s) (when applicable)

7.3.2.2 Pharmacokinetics

7.3.2.2.1 Pharmacokinetic Studies

When applicable depending on the type of vaccine or when new substances are used in the formulation of the product, novel adjuvant(s), new routes of administration, or pharmaceutical forms that require the respective pharmacokinetic evaluation.

7.3.2.3 Toxicology

7.3.2.3.1 General Toxicology

Information should be presented on:

- Design of the study and justification of the animal model
- Animal species used, age, group size
- Dose, route of administration, and control groups
- Parameters monitored
- Local tolerance

7.3.2.3.2 *Special Toxicology for Vaccines* (when applicable)

- Special immunological investigations
- Toxicity studies in special populations
- Genotoxicity and carcinogenicity studies, when applicable
- Reproductive toxicity studies for vaccines to be administered to pregnant women or individuals of fertile age.

7.3.2.4 Special Considerations

7.3.2.4.1 Live Attenuated Vaccines

An evaluation should be presented of the possibility of microorganism shedding through natural avenues of excretion.

7.3.2.4.2 New Substance(s) incorporated into the formulation

New adjuvant(s), stabilizer(s), additive(s), other routes of administration, and new combined vaccines, submit the corresponding toxicology studies.

7.4 ASSESSMENT OF CLINICAL DATA

7.4.1 Advice to External Experts and DGDA team on Clinical Assessment

The following general aspects should be considered:

The Clinical assessment report should be sufficiently detailed to allow for secondary assessment by other experts and DGDA team.

Cross-references should be used to clearly indicate the origin of any information used in the Clinical assessment report, such as the specific parts of the dossier (e.g. overview, summary, study reports), references to the literature or other sources.

The Clinical assessment report should indicate whether findings have implications for human

safety.

The Clinical assessment report should also emphasize findings that need to be reflected in the SmPC.

For each main section of the Clinical assessment report should describe the data submitted.

For each type of study, after distinguishing between main and supportive data, it should be assessed whether the main data consist of all the particulars and documents of non-clinical and clinical study reports ('original data'), bibliographical references, a combination of the two, or if data are absent.

Where the data submitted deviate from the requirements, the acceptability of any justifications should be assessed. In particular, absence of any data for non clinical/clinical test or trials, or use of bibliographical references substituting in part or completely original data for main studies must be justified.

The following specific scientific aspects should be considered:

The Clinical studies should comply with the *'World Health Organization Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations'. WHO Technical Report Series No. 924, 2004,* which is replaced by recent version TRS 1004 annex 9 clinical evaluation vaccines or other equivalent International Guideline(s).

The scope of the assessment tasks to be performed by the Clinical assessment expert staffs is as follows:

(1) evaluate phase I+II clinical studies and ethical considerations. The Clinical expert staffs should be acquainted with the following issues: The phase I studies in small groups of healthy adults are intended to define dose and route of administration, to define the safety and reactogenicity and to seek preliminary information on immunogenicity. The phase II studies involve a larger number of subjects and are usually controlled and randomized and aimed to demonstrate immunogenicity and safety in the target population (mainly healthy children).

The phase II studies should also define the optimum dose, the vaccination schedule, and most importantly, safety, prior to beginning phase III. Special attention should be given to the ethical considerations underlying testing in special groups, such as children, elderly, male/female and ethnic minorities and in particular use of placebo controls or challenge tests.

Clinical expert staffs should also be qualified to evaluate reports of Phase III clinical studies and, if already performed, reports of Phase IV studies as well as methodological considerations according to clinical trial guidance documents. Phase III studies are designed to obtain data on the efficacy and safety in large populations, performed preferentially by using at least three

(3) vaccine batches manufactured at production scale. If a correlate of protection between clinical efficacy and immunogenicity is proposed, this should be thoroughly evaluated. If the clinical trial comprised for example interaction studies with other vaccines studies, or interference with maternal antibodies or microorganism shedding in the case of live vaccines, this will need another careful assessment. Important methodological considerations, such as case definition and detection, vaccination failures, sample size, statistical criteria and duration of follow-up must also be addressed in the AR.Trials performed with combined vaccines protecting against multiple infectious diseases; combined vaccines containing different strains or serotypes of a microorganism; and/or standard vaccines administered with new combined vaccines need additional considerations. The current success in developing new combination vaccines has very much complicated the evaluation of the clinical trials and the resulting vaccination schedules and continues to present unique challenges to vaccine manufacturers as well as regulatory authorities.

A combination vaccine may raise serious safety, efficacy and immunogenicity concerns due to manufacturing and formulation issues, due to increased reactogenicity but also due to immunologic interference, e.g. diminution of the immune response to one or more of the antigens or an undesired increase of the immune response.

Clinical expert staffs may contribute to the Clinical assessment report as follows:

(1) provide licensing recommendations based on clinical efficacy and/or immunogenicity aspects and provide comments to the Executive Summary describing whether the studies performed comply with the current WHO Clinical trial requirements or other equivalent International Guideline(s);

(2) provide comments to the scientific overview and discussion on clinical efficacy and/or immunogenicity aspects which summarize the salient results from the main studies. Any concerns raised during the Clinical assessment about compliance with Good Clinical Practice (GCP) or related regulatory and ethical requirements (e.g. data accuracy or protocol compliance and compliance with ethical aspects) should be specifically addressed here and the need for a GCP inspection be discussed.Additionally, Clinical expert staffs contribute to the Clinical assessment report as follows:

(3) provide recommendations on licensing conditions and product literature based on clinical efficacy and/or immunogenicity aspects.

The clinical safety evaluation of a vaccine includes information from controlled phase I-III or IV studies as well as from uncontrolled studies, i.e. the safety data should consider the experience available from all patients exposed and therefore should be

presented as an integrated analysis. The Clinical expert staffs should also recall concerns identified in non-clinical studies with potential for human use. The scope of the clinical assessment tasks to be performed in this context is as follows:

(4) evaluate clinical safety with regards to patient exposure, adverse events, reactogenicity, serious adverse events and deaths, laboratory findings, safety in special populations, safety related to vaccine-vaccine interactions, discontinuation due to adverse events;

(5) provide comments to the Clinical Overview in the areas of agreement /disagreement, which should be highlighted in the submitted dossier and

(6) provide comments on the suitability of the SmPC. The clinical safety assessment of combined vaccines, in addition to efficacy/ immunogenicity assessment, requires also a careful evaluation, regardless of whether or not the combination consists of previously marketed or investigational individual component vaccines. Clinical expert staffs should pay attention that safety of the new combination is not decreased in comparison to the safety of separate, but simultan eously administered individual components. Furthermore, for safety evaluation of combination vaccines, as much as possible information should be obtained from randomized, controlled trials. Where applicable, controls should be the already marketed vaccines with the same antigen composition. For vaccines intended for infants and children, defining differences in rates of high fever may be especially relevant

Clinical safety expert staffs may contribute to the Clinical assessment report as follows:

(7) provide licensing recommendations based on clinical safety aspects and provide comments to the Executive Summary describing whether the studies performed comply with the current WHO Clinical trial guidelines or other equivalent International Guideline(s) regarding their recommendations on clinical safety assessment;

(8) provide comments to the scientific overview and discussion on clinical safety aspects which summarize the salient results from the main studies;

9) provide recommendations on licensing conditions and product literature based on clinical safety aspects.Pharmacovigilance is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short-term side effects of medicinal products, including vaccines, in other words the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of a vaccine, aimed at preventing harm to patients. A future marketing authorization holder should ensure that the pharmacovigilance plan is in place and during the evaluation the Pharmacovigilance expert staffs control whether the pharmacovigilance plan as described in the licensing dossier fulfils the legislative requirements (if available). As vaccines are primarily used in healthy people, their safety must be excellent in order to be accepted. To monitor them after their

marketing is the unique way to detect rare adverse drug reactions (ADRs).

A standard recommendation sentence with regards to the review of data on Clinical aspects could read: *based on the review of data on Clinical the experts consider that the application for vaccine <product name> could be approvable provided that satisfactory responses are given to checklist.*

The Clinical expert staffs should also develop an overview section which is more focused, with discussion indicating any important or interesting issues and any concerns over the Clinical aspects of the product. If there remains any concerns with respect to Clinical aspects, it would be helpful if the Clinical expert staffs indicated whether these might for example be addressed by amending the SmPC.

7.4.2 Information on Clinical Data

7.4.2.1 General Comments

Before beginning the clinical studies, it is necessary to have in-depth knowledge of the epidemiology of the pathogens or disease of interest in the study population. This knowledge makes it possible to statistically define the size of the sample required for the studies and to weigh the magnitude of the results for efficacy and safety. All clinical studies should comply with the *'ICH GCP'* or *'WHO Guidelines for Good Clinical Practices'*.

The clinical studies necessary to evaluate the clinical efficacy of a vaccine that contains one or more new antigens can involve substantial requirements with regard to the size of the population, compared to known and previously evaluated antigens. It is reasonable to require immunogenicity and safety studies only for vaccines that contain known, widely-used antigens and where correlates of protection have been well established.

7.4.2.1 Reports of Clinical Studies

7.4.2.2.1 Phase I Studies

These are intended to define the safety and reactogenicity of the vaccine and to seek preliminary information on immunogenicity. Dose and route of administration should be evaluated with respect to these parameters. Generally these studies are conducted on small groups of immunocompetent healthy adults (50 to 200) who present low risk of being infected by the vaccine or related complications.

7.4.2.2.2 Phase II Studies

After the studies in phase I have been completed or sufficient information is obtained to demonstrate satisfactory results, the phase II studies can begin. The main distinction between the two phases, is that the phase II studies involve a large number (200 to 600) of subjects and are usually controlled and randomized. The main objectives of these studies are to demonstrate the immunogenicity of the active component(s) and safety in the target population (mainly healthy children). The phase II studies should define the optimum dose, the vaccination schedule, and most importantly, safety, prior to beginning phase III.

7.4.2.2.3 Phase III Studies

The Phase III studies are large scale studies designed to obtain data on the efficacy and safety of the vaccine. These studies are usually carried out in large populations to evaluate the efficacy and safety to the formulation(s) of the immunologically active component(s). Several thousand subjects can be enrolled in these studies (the number will be defined by the end point of the study). Serological data are collected (for at least one immunized population subgroup) with the idea of establishing a correlation between clinical efficacy and immunogenicity, although this cannot always be established.

The type of vaccine and other relevant factors (incidence of disease, immunological markers, and safety) will determine the duration of the follow-up on these studies and the number of participants.

The phase III clinical studies should be performed using at least three (3) lots manufactured on the industrial or production scale to be used routinely (in the majority of countries).

7.4.2.2.4 Special Considerations

Depending on the type of vaccine, apart from the clinical studies on immunogenicity, efficacy and reactogenicity, it may be necessary to evaluate microorganism shedding in the case of live vaccines, interaction with other vaccines, and interference with maternal antibodies.

7.4.2.2.5 Adjuvant(s)

Evidence and scientific support that justify the use of adjuvant(s), when applicable.

Phase IV Studies depending on the type of application for marketing authorization, approval in other countries, or depending on the type of vaccine, a phase IV study protocol or the results of studies that have already been performed, will be required.

For new vaccines, a pharmacovigilance plan should be presented.

Combined Vaccines or Vaccines Made by New Manufacturers

Submit information on bridging studies performed to ensure the non-inferiority of the vaccine under evaluation compared with the reference vaccine, supporting immunogenicity, reactogenicity, safety, and efficacy, when applicable.

8. RECOMMENDED CONDITIONS FOR MARKETING AUTHORIZATION AND PRODUCT INFORMATION

8.1 Conditions for the Marketing Authorization

For example: legal status, specific obligations and other follow-up measures.

8.2 Summary of Product Characteristics (SmPC)

Check & assess the information according to template of SmPC Doc no: NRA-MA-018/F01-01 (can be found in www.dgda.gov.bd) and current applicable SmPC guidelines of European union and WHO.

If specific comments are warranted, these should be incorporated in the complete version of the original SmPC highlighting the proposed changes. Any comments should be put in a boxed area within the text.

8.3 Labelling

Check the information & design of label (outer and inner) according to template for Package & labelling information and Patient Information Leaflet Doc no: NRA-MA-018/F02-01 (can be found in www.dgda.gov.bd).

If specific comments are warranted, these should be incorporated in the complete version of the original labeling highlighting the proposed changes. Any comments should be put in a boxed area within the text.

8.4 Patient Information Leaflet (PIL)

Check & assess the information according to following criteria:

- PIL should be written in both Bangla and English language.
- Product name & active substances should be written as per SmPC.
- Composition should be written as per SmPC.
- Pharmacology of medicinal products should be written with easy-to-understand words for patients and as per SmPC.

- Indication of medicinal products should be written with easy-to-understand words for patients and as per SmPC.
- Dosage and administration of medicinal products should be written with easy-to-understand words for patients and as per SmPC.
- All available listed contraindications as per innovator/internationally available PIL should be written.
- All available listed precautions as per innovator/internationally available PIL should be written.
- All available listed drug interactions as per innovator/internationally available PIL should be written.
- All available listed side-effects as per innovator/internationally available PIL should be written.
- Pregnancy and lactation should be written with easy-to-understand words for patients and as per SmPC.
- Storage condition should be written as per SmPC.
- Commercial pack should be as per template Doc. No: NRA-MA-018/F02-01 (can be found in www.dgda.gov.bd).

If specific comments are warranted, these should be incorporated in the complete version of the original PIL highlighting the proposed changes. Any comments should be put in a boxed area within the text. The DGDA team shall include the assessment of the results in their assessment reports, as well as a conclusion on the overall readability of the PIL.

9. APPENDICES
10. REFERENCES

10.1 EMEA Guidance Document <Co->Rapporteur Day 80 Critical Assessment Report. *OVERVIEW AND LIST OF QUESTIONS D80 Overview - Rev 3 – 2007*

10.2 EMEA Guidance Document <Co->Rapporteur Day 80 Critical Assessment Report. *QUALITY D80-Quality-Rev 2-2006.*

10.3 EMEA Guidance Document <Co->Rapporteur Day 80 Critical Assessment Report. *NON-CLINICAL D80-Non-Clinical-Rev 2-2006*

10.4 EMEA Guidance Document <Co->Rapporteur DRAFT Day 80 Critical Assessment Report. *CLINICAL D80-Clinical-Rev 2 -2006*

10.5 Pan American Network for Drug Regulatory Harmonization Working Group on Vaccines (VWG). Proposed Harmonized Requirements for the Licensing of Vaccines in the Americas. Guidelines for Preparation of Applications. *PANDRH Guidelines version 01/21/03/2008*

10.6 WHO Guidelines on Stability Evaluation of Vaccines.

10.7 WHO Guidelines on Non-Clinical Evaluation of Vaccines, *WHO TRS No. 927, 2005*

10.8 WHO Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations, *WHO TRS No. 924, 2004*

10.9 Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products. Geneva. WHO, 2003 *(WHO/BCT/QSD/03.01)*

10.10 Guidelines for national control authorities on quality assurance for biological products. *WHO TRS 822, 1992 Annex 2*

10.11 Guidelines on good clinical practice (GCP) for trials on pharmaceutical products. *WHO TRS 850, 1995 Annex 3*

10.12 Guideline for Production and Quality Control of Vaccines in Bangladesh.