

Guidance for Industry

Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product

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Guidance for Industry:¹

Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product

GENERAL INFORMATION

I. BACKGROUND

In the Federal Register of July 8, 1997, the Food and Drug Administration announced the availability of Revised Form FDA 356h, "Application to Market a New Drug, Biologic, or an Antibiotic for Human Use." This document provides guidance on the content and format of the Chemistry, Manufacturing, and Controls (CMC) and Establishment Description sections of a License Application for a vaccine or related product. Reagents for in vitro diagnostic use are outside the scope of this document.

II. DEFINITIONS

Vaccine or Vaccine Related Product

A vaccine is an immunogen, the administration of which is intended to stimulate the 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. Prophylactic vaccines are not currently recognized as specified biotechnology products in Title 21 Code of Federal Regulations 601.2.

Vaccine related products include in vivo diagnostic antigens, other microbial derived proteins such as asparaginase or toxins such as botulinum toxin. A diagnostic antigen is a crude or purified fraction isolated from microbial culture and intended for in vivo detection of an existing specific immune response, usually by intradermal or percutaneous skin testing, e.g., histoplasmin or coccidioidin.

¹ This guidance document represents FDA's current thinking on the content and format of the Chemistry, Manufacturing and Controls information and Establishment Description information for a vaccine or related product. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Drug Substance

The drug substance is the unformulated active (immunogenic) substance which may be subsequently formulated with excipients to produce the drug product. The drug substance may be whole bacterial cells, viruses, or parasites (live or killed); crude or purified antigens isolated from killed or living cells; crude or purified antigens secreted from living cells; recombinant or synthetic carbohydrate, protein or peptide antigens; polynucleotides (as in plasmid DNA vaccines); or conjugates. For combination vaccines, each active substance, which will be pooled, combined with other antigens and formulated, should be described.

Drug Product

The drug product is the finished dosage form of the product. The drug product contains the drug substance(s) formulated with other ingredients in the finished dosage form ready for marketing. Other ingredients, active or inactive, may include adjuvants, preservatives, stabilizers, and/or excipients. For vaccine formulation, the drug substance(s) may be diluted, adsorbed, mixed with adjuvants or additives, and/or lyophilized to become the drug product.

PART 1 – CHEMISTRY, MANUFACTURING AND CONTROLS SECTION

I. DRUG SUBSTANCE

Production of a drug substance, whether by fermentation, cultivation, isolation, or synthesis, usually starts with raw materials. Subsequent steps of the procedure involve preparation, characterization and purification of intermediates eventually resulting in the drug substance. The quality and purity of the drug substance cannot be assured solely by downstream testing, but depends on proper control of the manufacturing and synthetic process as well. Proper control and attainment of minimal levels of impurities depends on:

- appropriate quality and purity of the starting materials, including the seed organisms, and reagents;
- establishment and use of in-process controls for intermediates;
- consistent adherence to validated process procedures; and
- adequacy of the final (release) control testing of the drug substance.

A. Description and Characterization

This section should be completed for each drug substance identified as being present in the final drug product. For combination vaccines, referencing the approved license application may be acceptable.

1. Description

This section should contain a clear description of the drug substance. The biological name (including strain and/or clone designation) or chemical name, including any established USAN name, should be provided. The description should also include the source of the cells, including microbes, from which the drug substances were derived, the active components of the cell fractions or purified antigens, and the physical and chemical properties of the synthetic drug substance. Any chemical modification or conjugation of the drug substance should be described in detail. Also, a list of any inactive substances, which may be present in the drug substance, should be provided.

2. Characterization

This section should contain a description of all analytical testing performed to characterize the drug substance with respect to identity, purity, potency, and stability. (See references 2, 3, 7, 11-17, 19, 21). Test results should include actual data such as tabular data, legible copies of chromatograms or spectra, photographs of gels or immunoblots, actual histograms of cytometric analysis, or other appropriate formats. Data should be well organized and fully indexed to enable easy access. Results for quantitative assays should be presented as actual data, not generally as "Pass" or "Fail." Some tests listed below may not be necessary or applicable for all substances.

a. Physicochemical Characterization

In general, characterization may include, but is not limited to the following:

- UV/visible or mass spectrometry;
- amino acid analysis;
- amino acid or nucleic acid sequencing;
- carbohydrate analysis and, if appropriate, sequencing;
- peptide mapping;
- determination of disulfide linkage;
- Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) (reduced and non-reduced);
- isoelectric focusing (1D or 2D);
- various chromatographic methods such as HPLC, GC, LC, or thin layer chromatography;
- nuclear magnetic resonance spectroscopy; and/or
- assays to detect related proteins including deamidated, oxidized, processed, and aggregated forms and other variants, such as amino acid substitutions and adducts/derivatives, and other process contaminants such as sulfhydryl reagents, urea, residual host proteins, residual DNA, and endotoxin.

Additional physicochemical characterization may be required for modified drug substances such as conjugates, multiple antigen peptides (MAP), or those undergoing further chemical or enzymatic modifications. The information provided should include the degree of derivatization or conjugation, the amount of unmodified substance, removal of free materials (e.g., toxins, linkers, etc.), and the stability of the modified substance.

b. Biological Activity

Further characterization of vaccines may include, but is not limited to the following:

- specific identity testing such as Western blot analysis or ELISA;
- cytometric analysis;
- neurovirulence testing, if appropriate;
- serotyping;
- electrophoretic typing;
- inactivation studies;
- neutralization assays; and
- titrations.

A description and results of all relevant in vivo and in vitro biological testing (bioassays) performed on the manufacturer's reference standard lot or other relevant lots to demonstrate the potency and activity(ies) of the drug substance should be provided. This section should include a complete description of the protocol used for each bioassay, the control standards used, the validation of the inherent variability of the test, and the established acceptance limits for each assay. The characteristics of specific antibodies used in the immunochemical or serological assays should also be included.

B. Manufacturer

1. Identification

The application should include the name(s), address(es), FDA registration number, and other pertinent organizational information for each manufacturer responsible for any portion of the manufacture or testing operations for the drug substance. This may include independent contractors or other company subsidiaries serving as contractors, or other locations/sites owned and operated by the applicant. Also included in this section should be a discussion of the operations performed by each party and the responsibilities delegated to each party by the applicant.

2. Floor Diagram(s)

For each manufacturing location, a simple floor diagram of the general layout of the facilities, which traces the drug substance through the manufacturing process should be

included. This diagram need not be a detailed engineering schematic or blueprint, but rather a simple drawing that clearly depicts the relationship of each manufacturing area, suite, or room to the others. The uses made of adjacent areas that are not the subject of the application should also be included. The diagrams should be sufficiently clear to enable visualization of the production flow and to identify adjacent operations that may create particular concerns, e.g., the proximity of live viral cultures to inactivated intermediates or final products, segregation of animal facilities, etc. Room numbers or other unique identifiers should be clearly indicated. Reference can be made to the manufacturing flow chart in section I.C.2.

3. Manufacture of Other Products

A comprehensive list of all additional products that are manufactured or manipulated in the same areas used to produce the drug substance that is the subject of this application should be provided. This section should include a brief description of the type and developmental status of the additional drug substances/products and indicate the areas into which these other products will be introduced, whether on an ongoing or campaign basis, and what manufacturing steps will be performed in the multiple-use area(s). Also, the applicant should indicate whether the production of other products will utilize the same product contact equipment and, if so, how that equipment will be cleaned and validated between operations for the manufacturing of different products. Data should be provided for the validation and cleaning in the appropriate section.

4. Contamination Precautions

For all areas in which operations for the preparation of cell banks and product manufacturing are performed, including areas for the handling of animals used in production, the following information concerning precautions taken to prevent contamination or cross-contamination, should be provided:

- air quality classification of a room or area in which an operation is performed, as validated and measured during operations;
- a brief, narrative description of the procedures and/or facility design features for the control of contamination, cross contamination, and containment (air pressure cascades, segregation of operations and product, etc.) - this is of particular importance for multi-use areas or for work with live organisms;
- general equipment design description, e.g., does design represent an open or closed system or provide for a sterile or non-sterile operation; and
- a description of the in-process controls performed to prevent or to identify contamination or cross contamination. The manipulation of more than one cell line in a single area, or the use of any piece of equipment for more than one cell line, should be indicated and measures to ensure prevention of cross contamination should be discussed.

C. Method of Manufacture

This section should be completed for each drug substance described in I.A. A detailed description of the manufacturing and controls should be provided to demonstrate proper quality control and prevention of possible contamination with adventitious agents. The inclusion of a list of all relevant SOPs is recommended; however, actual copies of the SOPs are not required.

1. Raw Materials

A list of all materials (culture media, buffers, resins for peptide synthesis, chemicals, columns, etc.) used in the manufacture of the drug substance, and their tests and specifications, or reference to official compendia, should be provided. For purchased materials, representative certificates of analysis from the supplier(s) and/or manufacturer's acceptance criteria should be provided. Redundant testing at the purchasing manufacturer may not be necessary if the testing methods at the vendor are approved by the purchasing manufacturer. Custom reagents, such as monoclonal antibodies, enzymes, other proteins, uncommon amino acids and derivatives, or glycolipids, used in purification or production of the drug substance, should be described in detail, including identification of the vendor/supplier, specificity, and origin, including the manufacturing scheme, if applicable (references 3, 11, 14, 16). Results of adventitious agent testing of raw materials used in propagation, e.g., serum, trypsin, should be provided. Process gases (compressed air, carbon dioxide, nitrogen) and water are considered raw materials. This list should be referenced in parts of the Application which provide detailed descriptions of the use of each component (see I.C.4, Batch Records).

2. Flow Charts

In this section, a complete visual representation of the manufacturing process flow should be provided for each drug substance. For multiple drug substances prepared from a single strain, a common flow chart is acceptable, through the propagation and harvest cycle, with indications of where the processing diverges. This flow chart should show the steps in production, equipment and materials used, room or area where the operation is performed (may reference diagrams in other sections of the application), and a complete list of the in-process controls and tests performed on the product at each step. In-process holding steps should be included, with time and temperature limits indicated. For chemical synthesis, a flow chart should include all the steps in a general synthesis cycle with other specific steps, such as fragment condensation or peptide cleavage, indicated. This diagram should also include information (or be accompanied by a descriptive narrative) on the methods used to transfer the product between steps, (e.g., open transfers under laminar flow units). Such transfers should be described for movement of product between equipment, areas, rooms, buildings and sites. Manufacturing steps which are computer controlled should be identified. Reference may be made to other sections of the application for more detailed process information. If equipment is dedicated to specific areas or products, it should be identified.

3. Detailed Description

a. Animal Sources (including fertilized avian eggs)

Detailed information on any animals used for the propagation of microorganisms, or production of recombinant proteins (reference 12), for use as vaccines should include, but is not limited to:

- the species and age of the animals;
- the health status of the animals, e.g., specific pathogen free;
- the results of adventitious agent screening;
- the animal husbandry practices, e.g., quarantine procedures, used to ensure the suitability of the animals;
- the veterinary and laboratory monitoring used to ensure the suitability of the animals;
- a description of the inoculation of the animals; and
- a description of the tissues harvested and the method of harvest.

b. Virus Sources

This section should include a detailed description of the virus seed used for vaccine production. The information submitted should include, but is not limited to:

- the original source of the virus
- the passage history of the virus strains
- details of the seed lot system
- the culture techniques for virus seed maintenance

c. Cellular Sources

For the purposes of this document, cell substrate refers to microbial cells, or cells or cell lines of animal (insect, as well as human and other mammalian) origin (references 13, 21). Cell seed lot systems are frequently adopted for cells or cell lines, whether they are used as vaccine components (whole cells or subunits), or as the cell substrate for propagation of viruses, recombinant DNA products, or polynucleotide vaccine constructs. Details of the cell seed lot system should be submitted as explained in iv. of this section. The history and general characteristics of the cell lines should be provided. All specific procedures used to generate the cell substrate should be well documented and submitted as outlined in the following sections. These may include, for example, cell fusion, selection, transfection, colony isolation, cloning, gene amplification, and adaptation to specific culture conditions or media. The growth pattern and morphological appearance of the cell lines, from the master cell bank to the end-of-production cells, should be submitted. A thorough discussion of the adventitious agent profile of any cell substrate should be provided.

i. Microbial Cells

This section should contain a description of the species, strain and known genotypic and phenotypic characteristics of the microorganism from which the drug substance is derived. Microbial cells and their derivatives used as the vaccine drug substance include whole cell vaccines (live or killed), crude lysate or purified immunogens, recombinant DNA products, conjugates, and plasmid DNA vaccines.

The history and characteristics of each strain used to produce the product and a complete strain description should be provided, including:

- origin of isolate;
- species;
- biochemistry (fermentation profile, etc.);
- strain identifier and specific identifying characteristics (serotype, etc.);
- virulence (attenuation method, if performed);
- genetic characterization, if known (markers, inserts, deletions, etc.);
- plasmids; and
- genetic stability.

ii. Animal Cells

Cells of animal origin may harbor adventitious agents and consequently pose a potentially greater risk to humans if not properly controlled (reference 21). The measures taken to remove, inactivate, or prevent contamination of the product from any adventitious agent present in the cell substrate should be described.

Primary Cells

This category generally includes the primary cells and those used within the first passage after establishment from the tissue of origin. Consequently, primary cells may not be amenable to the establishment of cell banks. A discussion of the rationale for the use of primary cells should be provided. The information submitted for each primary cell line used should include, but is not limited to:

- the species and age of the animals and the source tissue from which the cells are derived;
- the health status of the animals from which the cells are derived, e.g., specific pathogen free;
- the animal husbandry practices (quarantine, etc.) used to ensure the suitability of the animals;
- the veterinary and laboratory monitoring used to ensure the suitability of the animals;
- a description of the preparation of primary cell substrates; and

- an explanation of the concurrent testing done to demonstrate the absence of adventitious agents and the results of those tests.

Cell Lines

The production substrate may consist of a continuous cell line or diploid cell strain of human or animal origin. For human cell substrates, the source of cells should be clearly described, including the materials and methods used, the tissue or organ of origin, ethnic and geographical origin, age, gender and general physiological condition. The health or medical history of the donor, if known, should be provided along with the results of any tests for pathogenic agents. For animal cell lines, relevant descriptions of the source may include species, strains, breeding conditions, tissue or organ of origin, geographical origin, age, gender, and general physiological condition of the original donor. Testing for detection of adventitious agents should be undertaken with consideration of the possible agents which may be present in the cells. Results of all testing should be included.

iii. Genetic Constructs and Recombinant Cell Lines

For recombinant DNA (rDNA) derived products and rDNA-modified cell substrates, detailed information should be provided regarding the host cells, and the source and function of the component parts of the recombinant gene construct (references 7, 13-16, 19, 21), including:

Host Cells

A description of the source, relevant phenotype, and genotype should be provided for the host cell used to construct the biological production system. The results of the characterization of the host cell for phenotypic and genotypic markers, including those that will be monitored for cell stability, purity, and selection should be included.

Gene Construct

A detailed description of the gene which was introduced into the host cells, including both the cell type and origin of the source material, should be provided. A description of the method(s) used to prepare the gene construct and a restriction enzyme digestion map of the construct should be included. The complete nucleotide sequence of the coding region and regulatory elements of the expression construct, with translated amino acid sequence, should be provided, including annotation designating all important sequence features.

Vector

Detailed information regarding the vector and genetic elements should be provided, including a description of the source and function of the component parts of the vector, e.g. origins of replication, antibiotic resistance genes, promoters, enhancers. A restriction enzyme digestion map indicating at least those sites used in construction of the vector should be provided. The genetic markers critical for the characterization of the production cells should be indicated.

Final Gene Construct

A detailed description should be provided of the cloning process which resulted in the final recombinant gene construct. The information should include a step-by-step description of the assembly of the gene fragments and vector or other genetic elements to form the final gene construct. A restriction enzyme digestion map indicating at least those sites used in construction of the final product construct should be provided.

Cloning and Establishment of the Recombinant Cell Lines

Depending on the methods to be utilized to transfer a final gene construct or isolated gene fragments into its host, the mechanism of transfer, copy number, and the physical state of the final construct inside the host cell (i.e. integrated or extrachromosomal), should be provided. In addition, the amplification of the gene construct, if applicable, selection of the recombinant cell clone, and establishment of the seed should be completely described.

iv. Cell Bank System

A description of the cell banking procedures used should be provided, including:

- the banking system used;
- the size of the cell banks;
- the container and closure system used;
- a detailed description of the methods, reagents and media used for preparation of the cell banks;
- the conditions employed for cryopreservation and storage;
- in-process controls; and
- storage conditions.

A description should be provided of the procedures used to avoid microbial contamination and cross-contamination by other cell types present in the facility, and the procedures that allow the banked cells to be traced. A discussion of precautions

taken to prevent any catastrophic event that could render the cell banks unusable and to ensure continuous production of vaccines, for example, storage of cell banks in multiple freezers or at different sites, should be included. The cell bank system generally consists of two tiers: a Master Cell Bank (MCB), and a Working Cell Bank (WCB) generated from the MCB for vaccine manufacturing. In some instances, another tier of 'Primary Cell Bank' may be established which allows the manufacturers to perform extensive testing on a pool of cryopreserved primary cells prior to their usage in vaccine production.

Master Cell Bank

The cells comprising the MCB should be identified and a complete history and characterization of the MCB should be provided, including, as appropriate for the given cells:

- the biological or chemical method used to derive the cell bank;
- biochemistry (cell surface markers, isoenzyme analysis, specific protein or mRNA, etc.);
- specific identifying characteristics (morphology, serotype, etc.);
- karyology and tumorigenicity;
- virulence markers;
- genetic markers;
- purity of culture; and
- media and components (e.g., serum).

For recombinant products, the cell substrate used to establish the MCB is the transfected cell containing the desired genetic construct which has been cloned from a single cell progenitor. For non-recombinant products, the cell substrate is the cell from the parental cell line chosen for preparation of the MCB without further modification. For a diploid cell line the population doubling level chosen for the MCB should be given.

Working Cell Bank

This section should contain a description of the procedures used to derive a WCB from the MCB. The description should include the identification system used for the WCB as well as the procedures for storage and cataloging of the WCB. The assays used for qualification and characterization of each new WCB should be included with the results of those assays for the WCB currently in use. If applicable, a description of animal passage of the WCB performed to assure the presence of virulence factors which are protective antigens should be supplied. This section should also contain a description of the methods and procedures used to assure culture purity and identity.

End of Production Cells (EPC)

For r-DNA derived drug substances, a detailed description of the characterization of the EPC that demonstrates that the biological production system is consistent during growth should be provided. The results of the analysis of the EPC for phenotypic or genotypic markers to confirm identity and purity should be included. This section should also contain the results of testing supporting the freedom of the EPC from contamination by adventitious agents. The results of restriction enzyme analysis of the gene constructs in the EPC should be submitted. Further guidance can be obtained from the ICH document on "Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products".

Characterization and Testing of Cell Banks

Detailed information on the characterization and testing of banked cell substrates should be submitted (references 7, 13-16). This should include the results of testing to confirm the identity, purity, and suitability of the cell substrate for manufacturing use. Relevant tests should be described in the Application, along with the results of the testing. In general, the methods described in Section I.A.2.a. are considered adequate tests to confirm the identity and purity. For metazoan cells, results of tests for the presence of bioburden (bacteria and fungi) and mycoplasma should be submitted for the MCB and WCB. The results of virus testing of metazoan cell substrates to detect possible contaminating viruses, using appropriate screening tests designed to detect a wide spectrum of viruses and relevant specific tests based on the cultivation history of the cell line, should be submitted. Further guidance may be obtained from the "Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals, 1993."

v. Cell Growth and Harvesting

This section should contain a description of each of the following manufacturing processes, as appropriate. The description should contain sufficient detail to support the consistency of manufacture of the drug substance. It is understood that all of the processes listed below may not be performed on every drug substance, or be performed in the order given. A description of the assignment of batch numbers and how each batch of a stabilized intermediate containing multiple drug substances can be related to its component harvests and batches of individual drug substances should be included.

Propagation

This section should contain descriptions of:

- each step in propagation from retrieval of the WCB to culture harvest (stages of growth);
- the media used at each step (including water quality), with details of their preparation and sterilization;
- the inoculation and growth of initial and sub-cultures, including volumes, time and temperature of incubation(s);
- how transfers are performed;
- precautions taken to control contamination;
- in-process testing which determines inoculation of the main culture system;
- in-process testing to ensure freedom from adventitious agents, including tests on culture cells, if applicable;
- the nature of the main culture system including operating conditions and control parameters (e.g., temperature of incubation, static vs. agitated, aerobic vs. anaerobic, culture vessels vs. fermenter, volume of fermenter, or number and volume of culture vessels);
- the parallel control cell cultures, if applicable, including number and volume of culture vessels;
- induction of antigen, if applicable; and
- the use of antibiotics in the medium and rationale, if applicable.

A brief description of all process parameters which are monitored and a typical growth curve or growth description (see Process validation, I.D.2) should be provided. A list of in-process controls and testing for purity, viability, antigen yields, and phenotypic identity; as well as the time points at which testing is performed should be included in both the Flow Chart (Section I.C.2.) and the Batch Records (Section I.C.4.). A description should be provided of the precautions taken to control contamination, e.g., during sample removal and transfers, and whether these are "closed" or "open" procedures.

Harvest

A description of the method(s) used for separation of crude drug substance from the propagation system (precipitation, centrifugation, filtration, etc.) should be provided. Brief descriptions should be given for the following:

- the process parameters monitored;
- the criteria for harvesting;
- the determination of yields; and
- the criteria for pooling more than one harvest, if applicable.

This section should include a working definition of a harvest "batch." A description should be provided of the precautions taken to maintain aseptic conditions and prevent contamination during harvesting. A description of the procedures used to monitor bioburden (including acceptance limits) or sterility should be included. If the harvested crude drug substance is held prior to further

processing, a description of storage conditions and time limits should be provided.

d. Purification and Downstream Processing

This section should contain a description of the methods and materials by which intermediate forms and the final bulk of the drug substance are separated and concentrated from the cells, media, solvents or solutions used in the production process. The description of each step of the purification process should also include the accompanying analytical tests developed or adopted by the manufacturer to show identity, purity, and concentration, and the levels of product related and non-product related impurities. This is particularly important if the latter materials are determined to be toxins, carcinogens, teratogens, or allergens. Antibiotics and other components (e.g., growth factors, antibodies) used in the culture but neither required nor specifically intended to be in the final vaccine product should be removed before use. Procedures to assure containment and prevention of contamination or cross contamination should be provided.

i. Inactivation (if appropriate)

Descriptions should be provided for:

- how culture purity is verified before inactivation;
- the method(s) and agent(s) used for inactivation;
- the method(s) undertaken to prevent aggregation and assure homogeneous access of inactivating agent(s).
- the stage in production where inactivation or killing is performed; and
- the parameters which are monitored.

Verification of the adequacy of and margin of safety achieved by the method of inactivation or killing should be provided (see I.D.2., Process Validation).

ii. Purification (if appropriate)

This section should contain an explanation of the objectives and rationale for purification of component antigens from crude harvest. Descriptions should be provided for:

- the methods used, including specialized equipment such as columns; ultracentrifugation, ultrafiltration, and custom reagents such as monoclonal antibodies;
- the process parameters monitored;
- the determination of yields;
- in-process testing (e.g., sensitivity and specificity of ELISA);
- the criteria for pooling more than one batch, if applicable;

- sterility or bioburden monitoring and the precautions taken to prevent contamination during purification;
- the reuse and/or regeneration of columns and adsorbents; and
- monitoring for residual impurities and leachable reagents.

A list of in-process controls and tests for purity, identity, and biological activity should be provided. The time points at which testing is performed should be included in both the Flow Chart (Section I.C.2) and the Batch Records (Section I.C.4.). A list of the final acceptance criteria for the purified drug substance should be provided. If the purified drug substance is held prior to further processing, a description of the storage conditions and time limits should be included. Verification of the stability of the purified substance under the conditions described should be included (see I.D.2, Process Validation).

iii. Stability Processing

A description should be provided for any post-purification steps performed to produce a stabilized intermediate, (e.g., adsorption, addition of stabilizers, addition of preservatives, lyophilization (in bulk), desiccation), and the objectives and rationale for performing each process. A description of precautions taken to monitor bioburden and prevent contamination during these processes should also be given. If the stabilized intermediate is held prior to further processing, a description of storage conditions and time limits should be included. Verification of the stability of the drug substance under the conditions described should be provided (see I.D.2, Process Validation).

iv. Detoxification

For toxoid or toxoid-containing vaccines, the detoxification procedures should be described in detail for the toxin component(s):

- the method(s) and agent(s) used for detoxification;
- the stage in production where detoxification is performed; and
- the parameters which are monitored.

Verification of the adequacy of the method for detoxification should be provided (see I.D.2, Process Validation).

e. Synthetic Drug Substance

For the purposes of this guidance, synthetic drug substance includes: linear or complex synthetic peptides, or modified synthetic or semi-synthetic immunogens such as lipopeptides, peptide to carrier protein or polysaccharide to carrier protein conjugates.

i. Synthetic Peptides

The detail of the peptide synthesis including purification procedures should be provided as outlined in the “Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances”.

ii. Conjugates and Modified Drug Substance

This section of the guidance refers to drug substances derived from another drug substance or intermediate through chemical or enzymatic modification, e.g., conjugation of an immunogen to a carrier molecule, enzymatic or chemical cleavage and purification of the non-toxic subunit of a toxin, or derivatization. The modification may change the fundamental immunogenicity, toxicity, stability, or pharmacokinetics of the source drug substance. The derived drug substance may include linking moieties and new antigenic epitopes.

Manufacturing Methods

This section should provide a detailed description of:

- the specifications and acceptance criteria, for the native drug substance starting materials, which assure suitability for conjugation or modification;
- the conditions of all reactions and/or syntheses used to produce a semi-synthetic conjugated molecule, derivatized molecule, or subunit, including intermediate forms of the reactants and drug substance; also include the process parameters which are monitored, in-process controls, testing for identity and biologic activity, and any post-purification steps performed to produce a stabilized derived drug substance.

The application should include a description of the methods and equipment used for separation of unreacted materials and reagents from the conjugate, derivative, or subunit, and a rationale for the choice of methods.

Specifications

Specifications should be provided for each modified drug substance, including identity, purity, potency, physical-chemical measurements, and measures of stability. If test results for the derived substance will be reported for final release of the drug product, a validation report, to include estimates of variability and upper and lower limits, should be provided for each specification. Specifications should include the amount of unreacted starting materials and process reagents unless their removal has been validated.

4. Batch Records

A completed (executed) representative batch record of the process of production of the drug substance should be provided.

D. Process Controls

1. In-process Controls

For all in-process testing indicated in the Flow Charts, a brief description of the sampling procedures and the test methods used should be provided. For testing performed at significant phases of production, the criteria for accepting or rejecting an in-process batch should be specified.

2. Process Validation

A summary report, including protocols and results, should be provided for the validation studies of each critical process or factor that affects drug substance specifications, i.e., a decision to accept or reject a batch (see "Guideline on General Principles of Process Validation, 1987" and references 2, 3, 7, 12, 14, 16, 17). The validation study reports with statistical rigor should document the variability in each process as it relates to final specifications and quality.

a. Propagation

A growth curve or tabular representation of growth characteristics for each propagation step, based on historical performance under specified conditions, should be provided. Data should be included which demonstrate the efficiency of induction of antigen production, if applicable. Data should also be provided showing the stability of genetic markers under the conditions of propagation, if applicable.

b. Harvest

For each method or combination of methods, a tabulation should be provided of yields, purity, and viability (if applicable) of the crude harvest, based on historical performance.

c. Inactivation

Inactivation or killing curves, or a tabular representation, based on historical performance should be provided. Validation of the titration method to measure residual live agents, including sensitivity in a background of inactivated agents, should be provided.

d. Purification

For each method or combination of methods used, a tabulation of yields, purity, and biological activity should be provided. Verification of the removal or dilution of product related and non-product related impurities, e.g., processing reagents, endotoxin, contaminating cell proteins or nucleic acids, and other residual contaminants should be included. A standard denominator (e.g., international units) should be used to facilitate comparison through processing, concentration, or dilution.

e. Microbiology

A description and documentation of the validation studies for any processes used for media sterilization, effectiveness of preservatives, decontamination, inactivating cells prior to their release to the environment, if such inactivation is required, etc., should be provided. If the drug substance is intended to be sterile, information should be submitted as described in the "Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products."

3. Control of Bioburden

For each process which is not intended to be sterile, documentation of the control of extraneous bioburden by a tabulation of in-process testing for bioburden should be provided. (Validation of bioburden control techniques may be described under Item 15 of the Application.) For aseptic processing, further guidance may be found in the "Guideline on Sterile Drug Products Produced by Aseptic Processing."

E. Manufacturing Consistency

Consistency of the manufacturing process for each vaccine component should be demonstrated by manufacturing at least three, preferably consecutive, batches of drug substance. The establishment and use of reference standards in assuring consistency in product characteristics should be described.

1. Reference Standards

A description of the preparation, characterization, and stability of primary and working reference standards should be provided. A detailed description of the procedures to qualify new lots of reference standards and acceptance criteria for a new reference standard should be included.

2. Release Testing

Release (acceptance criteria) testing results and other (for information only) characterization data (e.g., certificates of analysis) for each batch should be submitted.

F. Drug Substance Specifications

1. Specifications

This section should contain the specifications and tests for each drug substance. These should include assays for identity, purity, potency (biologic effect), physicochemical measurements which predict potency, and where applicable, measures of stability. For highly purified substances, purity in reference to the theoretical composition should be presented. In some cases test results for the stabilized intermediates of component antigens should be included in the final release of the drug product. The results of the validation studies for each of these specifications, including estimates of variability and upper and lower limits, should be provided. Where appropriate, potency should be presented relative to the respective U.S. Reference Standard as defined in 21 CFR 610.20.

2. Impurities Profile

This section should include a discussion of the impurities in the drug substance. The identity and quantity of impurities should be provided along with the analytical data (gels, elution profiles, Western blots, etc.) which support the impurities profile. Impurities that should be characterized and quantitated include:

- product related impurities (variants or alterations of antigen occurring during processing or storage)
- Process related impurities
 - media components;
 - cell substrate proteins or nucleic acids; or
 - process reagents which have not been removed by the purification process (see I.D., Process Controls).

G. Reprocessing

This section should include detailed information on any reprocessing that may be done on each drug substance. The information provided for each reprocessing procedure should include:

- a description of the conditions or criteria, determined from process controls or specifications, which indicate the need for re-processing;
- a description of the reprocessing step;
- the Standard Operating Procedure for the step;

- a description of any additional or modified in-process controls or specifications which are included to monitor re-processing steps;
- a description of the modifications in batch numbers and documentation of re-processing in the Batch Production Record (BPR); and
- the evidence derived from validation studies which assures that product identity, purity, potency, and stability is preserved for re-processed batches.

H. Container and Closure System

A description of the container and closure system, and its compatibility with the drug substance should be submitted. The submission should include detailed information concerning the supplier, address, and the results of compatibility, toxicity and biological tests. Alternatively, a Drug Master File (DMF) may be referenced for this information. If the drug substance is intended to be sterile, evidence of container and closure integrity for the duration of the proposed expiry period should be provided.

I. Drug Substance Stability

This section should contain information on the stability of the drug substance and any in-process material at each holding step, as outlined in “Stability Testing of New Drug Substances and Products, 10/27/93,” “Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products, 11/30/95” and “Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics, 1987.”

II. DRUG PRODUCT

This section should contain information on the final drug product including all drug substances and excipients in the final product. If any proprietary preparations or mixtures are used as components, the information provided should include a complete statement of composition and other information that will properly describe and identify these materials. For all ingredients of human or animal origin, testing results or certificates of analysis demonstrating their freedom from adventitious agents should be provided. Appropriate information may be cross-referenced to those under Drug Substance.

A. Composition and Characterization

1. Composition

A list should be provided of all components in the drug product, including drug substance(s) and other ingredients, with their unit doses and batch quantities specified. For some inactive ingredients, the quantity may be expressed as percent or molarity.

a. Drug Substance(s)

A list of each drug substance should be provided.

b. Excipient

This section should contain a list of all inactive components with the rationale for the inclusion of each in the final product. The information provided should include certificates of analysis, results of analytical testing, or other information that will describe or identify each excipient. If compendial excipients are used, citations may be included *in lieu* of analytical testing. Excipients may include, but not be limited to:

- diluents (molarity, pH should be included for these);
- bulking agents;
- adsorbents (other than adjuvants); and
- stabilizers (e.g., sugars, wetting agents).

c. Adjuvant

This section should contain a list of the chemical formula and precise quantity of each adjuvant per unit dose. Whether the quantity of adjuvant is determined by assay or by calculation should be indicated and the method used should be described.

d. Preservative

Each preservative should be identified by chemical as well as any trade name or reference to compendial sources. A rationale should be provided for the inclusion of a preservative in single dose drug products. The results of the preservative effectiveness studies should be included or reference may be made to other files.

2. Specifications and Analytical Methods for Drug Product Ingredients

This section should contain a description of tests and specifications for all ingredients, if not specified in the Drug Substance section.

a. Description

A qualitative statement describing the physical state (lyophilized solid, powder, liquid) and color and clarity of the drug product and other ingredients should be provided.

b. Identity

The assays used to establish the identity of the drug product should be described. The description of each assay should include an evaluation of its specificity and sensitivity.

c. Purity and Impurities

This section should include information on the purity of the final product including identification and quantitation of impurities, including degradation products, inherent in the final dosage form. If impurities are known to be introduced or formed during the production of the drug product, the acceptable limits of these impurities should be determined and included in the specifications.

d. Potency

A description should be provided of the potency assay for the drug product. Information should be submitted on the sensitivity, specificity, and variability of the assay including the data from the material used to prepare clinical/preclinical lots which were used to set the acceptance limits for the assay.

B. Manufacturer and Facilities

The name(s) and address(s) of all manufacturers involved in the manufacture and testing of the drug product including contractors, and a description of the responsibility(ies) of each should be submitted. A list of all other products (research & development, clinical or approved) made in the same rooms should be provided. See Part 1, Section I. B. of this document for detailed guidance.

C. Manufacturing Methods

This section should include a detailed description of the manufacturing process flow of the formulated bulk and finished drug product including the sterilization operations, aseptic processing procedures, lyophilization, and packaging. Accompanying this narrative, a flow chart should be provided that indicates the production step, the equipment and materials used, the room or area where the operation is performed (may reference the simple floor diagram) and a listing of the in-process controls and tests performed on the product at each step. A Master Production Record (MPR) for the drug product should be provided, including complete manufacturing instructions for adsorption (if applicable), formulation, filling, labeling, and packaging. References may be made to other sections for more detailed information. Results of studies validating the compatibility of the components including the adjuvants and/or preservatives, if applicable, should be provided. Lot-to-lot consistency of the drug product should be demonstrated.

D. Drug Product Specifications

1. Sampling Procedures

The sampling procedures for monitoring a batch of finished drug product should be included.

2. Specifications and Methods

A description of all test methods selected to assure the identity, purity, strength and/or potency, as well as the lot-to-lot consistency of the finished product and the specifications used for the drug product should be submitted. Certificates of analysis and analytical results for at least three consecutive batches should be provided.

3. Validation Results

The results of studies validating the specificity, sensitivity, and variability of each method used for release testing should be provided. Where applicable this should include descriptions of reference standards and their validation. For analytical methods in compendial sources, the appropriate citations should be provided.

E. Container and Closure System

A description of the container and closure system, and its compatibility with the drug product should be submitted. Detailed information concerning the supplier(s), address(es), and the results of compatibility, toxicity and biological tests should be included. Alternatively, a DMF can be referenced for this information. For sterile product, evidence of container and closure integrity should be provided for the duration of the proposed expiry period.

F. Microbiology

Information should be submitted as described in the "Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products."

G. Lyophilization

A validation summary for lyophilization of the drug product should be given which includes:

- A narrative description of the validation (or protocol);
- Certification that IQ and OQ have been completed;
- A validation data summary;
- Explanation of all excursions or failures; and
- Deviation reports and results of investigations of all excursions or failures.

H. Drug Product Stability

This section should state the proposed expiration dating period for the drug product and the recommended storage conditions. The criteria for determining the date of manufacture, from which the expiration dating period begins, should be defined. For lyophilized products, a shelf-life after reconstitution should be proposed. Detailed guidance on stability may be found in

“Stability Testing of New Drug Substances and Products, 10/27/93,” “Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products, 11/30/95” “Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics, 1987,” and “Guidance for Industry: Stability Testing of Drug Substances and Drug Products,” June 1998.

1. Stability Protocol

A stability study protocol should be provided which includes, but is not limited to, testing for:

- potency;
- physicochemical measurements which are potency-indicating;
- moisture, if lyophilized;
- pH, if appropriate;
- sterility or control of bioburden;
- viability of cells, if frozen and thawed;
- pyrogenicity; and
- general safety.

2. Stability Data

The summary results which support the proposed expiration dating period, under recommended conditions, in the final container and closure system, should be provided. The stability of each dosage form should be separately documented. For lyophilized products the data supporting the shelf-life of the product following reconstitution should be included. If the drug product is frozen, data supporting the stability of the product through a stated number of freeze-thaw cycles should be provided.

3. Stability Program

A plan for an on-going stability program should be provided. This should include the protocol to be used, number of final lots to be entered into the stability protocol each year and how such lots will be selected.

III. INVESTIGATIONAL FORMULATION

A discussion of any differences in formulation, manufacturing process, or site between the clinical trials materials and commercial production batches of drug substance and drug product should be submitted. If there are differences, a complete description of these differences should be included. If an investigational drug formulation was different from that of the to-be-marketed finished product, data to support comparability, bioequivalence and/or pharmacokinetic equivalence of the two formulations should be provided, if appropriate (reference 9). If the manufacturing process and/or site was different, data from appropriate testing to assess the comparability of the investigational and commercial products should be provided.

IV. ENVIRONMENTAL ASSESSMENT

An environmental assessment (EA), as outlined in 21 CFR Part 25, or a request for a categorical exclusion with the basis for the exclusion, should be submitted. If an EA is appropriate, it should include a description of the action that is being considered and should address all the components involved in the manufacture and disposal of the product.

V. METHOD VALIDATION

For all release or acceptance testing performed on the drug substance(s) or product, information as described in the “Guideline for Submitting Samples and Analytical Data for Methods Validation” should be provided.

PART 2 – ESTABLISHMENT DESCRIPTION SECTION

I. INTRODUCTION

In the Federal Register of July 8, 1997, the Food and Drug Administration announced the availability of Revised Form FDA 356h "Application to Market a New Drug, Biologic, or an Antibiotic for Human Use." This section provides guidance on the content and format of information submitted in Section 15, the Establishment Description section, of a License Application for vaccines and vaccine related products. The information contained in this section need not be submitted for recombinant DNA derived vaccines or synthetic peptide vaccines.

II. GENERAL INFORMATION

For each manufacturing location, a floor diagram should be included that indicates the general facility layout. The following information should be provided on each floor diagram and/or in an accompanying narrative:

- Product, personnel, equipment, waste and air flow;
- An illustration or indication of which areas are served by each air handling unit; and
- Air pressure differentials between adjacent areas.

Alternatively, this information may be illustrated on the floor diagram requested in the CMC section. The manufacturing flow chart requested in the CMC section may also be referenced as applicable.

III. SPECIFIC SYSTEMS

A. Water Systems

The following information on water purification systems for the production of water for use in manufacturing and rinsing of product contact equipment, and containers and closures, should be provided.

1. General Description

A general description of the water system(s) should be submitted, including water source, major components, and a general discussion of the type of water used for each stage of processing.

2. Validation Summary

A validation summary should be provided containing:

- a narrative description of the validation process (or protocol) including acceptance criteria;
- certification that installation qualification (IQ) and operational qualification (OQ) have been completed;
- the length of the validation period;
- the parameters monitored and tests performed;
- the frequency of monitoring each point of use during the validation period;
- a validation data summary; and
- an explanation of all excursions or failures, including deviation reports and results of investigations.

3. Routine Monitoring Program

A narrative description of the routine monitoring program should be submitted, to include:

- the tests performed;
- the frequency of testing;
- the alert and action limits used; and
- a summary of actions to be taken when limits are exceeded.

B. Heating, Ventilation, and Air Conditioning Systems (HVAC)

1. General Description

A general description of the HVAC system(s) should be provided including:

- the number and segregation of air handling units;

- whether air is once-through or recirculated;
- containment features; and
- air changes/hour.

The information required for some of these features is described below in greater detail in the contamination/cross contamination section of this document. Reference may be made to information in the CMC section.

2. Validation Summary

A validation summary with the following information should be provided for the system, which contains:

- a narrative description of the validation process (or protocol), including the acceptance criteria;
- certification that IQ, OQ and certification of filters has been completed;
- length of the validation period;
- a validation data summary (validation data should include Performance Qualification data accumulated during actual processing); and
- an explanation of all excursions or failures, including deviation reports and results of investigations.

3. Routine Monitoring Program

A narrative description of the routine monitoring program should be provided including:

- the tests performed and frequencies of testing for viable and nonviable particulate monitoring parameters;
- viable and nonviable particulate action and alert limits for production operations for each manufacturing area; and
- a summary of actions to be taken when limits are exceeded.

C. Computer Systems

This section should contain information on computer systems which control critical manufacturing processes. The developer of the system, i.e., whether in-house or contractor, should be identified. The information provided should also include a brief description of procedures for changes to the computer system. For each of these systems a list of the manufacturing steps which are computer-controlled should be provided. This section should also contain a validation summary for each of these systems, which includes:

- a narrative description of the validation process (or protocol), including acceptance criteria;
- certification that IQ and OQ have been completed;
- an explanation of the parameters monitored and tests performed;

- a validation data summary;
- an explanation of all excursions or failures; and
- deviation reports and results of investigations for all excursions or failures.

IV. CONTAMINATION/CROSS CONTAMINATION ISSUES

The following information regarding methods to prevent contamination and cross contamination should be provided to supplement the information requested in the CMC section of the application.

A. Cleaning procedures and validation

1. Dedicated Equipment

A brief description of the cleaning procedures and cleaning reagents used should be provided. This section should also contain a certification that the cleaning validation for removal of product residuals and cleaning agents has been successfully completed.

2. Shared Equipment

This section should contain:

- a brief description of the cleaning procedures and cleaning reagents;
- a rationale for the cleaning procedures chosen which addresses their effectiveness for the residual products to be removed; and
- a validation report describing the cleaning validation procedures for removal of product residues and cleaning agents. The report should identify the sampling and analytical methods used and address their sensitivities and specificities.

B. Containment features

This section should contain a description of segregation and containment procedures for areas, manufacturing operations, personnel, equipment and waste materials designed to prevent contamination of products. The features that are employed to maintain segregation and containment should be discussed. These features might include but is not limited to:

- air pressure differentials between adjacent manufacturing areas;
- segregation of air handling units;
- air supply and return (recirculated, once-through, HEPA filtered out, etc.); and
- use of airlocks

Reference may be made to information in the CMC section.

APPENDIX A

Guidance

1. Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, 1994
2. Guidance for Industry for the Evaluation of Combination Vaccines for Preventable Diseases: Production, Testing, and Clinical Studies, 1997
3. Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances, 1994
4. Guideline on Sterile Drug Products Produced By Aseptic Processing, 1987
5. Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics, 1987
6. Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, 1987
7. Guideline for Submitting Samples and Analytical Data for Methods Validation, 1987
8. Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use, 1996
9. FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products, 1996
10. Guideline on General Principles of Process Validation, 1987

Points To Consider

11. Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use , 1997
12. Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals, 1995
13. Points to Consider in the Characterization of Cell Lines Used to Produce Biologics, 1993
14. Points to Consider in the Production and Testing of New Drugs and Biologics Produced by Recombinant DNA Technology, 1985

15. Supplement to the Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology: Nucleic Acid Characterization and Genetic Stability, 1992

16. Points to Consider on Plasmid DNA Vaccines for Preventive Infectious Disease Indications, 1996

17. Points to Consider in Human Somatic Cell and Gene Therapy, 1991

International Conference on Harmonization (ICH) Guidelines

18. Stability Testing of New Drug Substances and Products, 10/27/93

19. Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products, 11/29/95

20. Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products, 11/30/95

21. Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin, 11/29/95

22. Guidance on Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products, 9/21/98