Guidance for Industry

Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Biological *In Vitro* Diagnostic Product

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U.S. Department of Health and Human Services
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Guidance for Industry: [1]

Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Biological *In Vitro* Diagnostic Product

GENERAL INFORMATION

I. INTRODUCTION

In the Federal Register of July 8, 1997 (62 FR 36558), 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 information to be submitted to the Chemistry, Manufacturing, and Controls (CMC) section and Establishment Description section of a License Application for a biological *in vitro* diagnostic (IVD) product.

This document is intended for use by those firms which manufacture any licensed *in vitro* diagnostics used to screen donor blood, determine donor suitability, test for retroviral infection, or determine transfusion compatibility. This document is not intended to cover those *in vitro* diagnostics for which a Pre-Market Application (PMA) or a 510K must be submitted. The "Guideline for the Manufacture of *In Vitro* Diagnostic Product" while designed to address products regulated by the Center for Devices and Radiological Health may provide information useful in preparing an application for licensure. It should be noted that some of the guidance documents included as references are directed primarily at injectable products and consequently certain of their recommendations, e.g., those concerning endotoxin testing, are not appropriate for IVD products. This document, the associated references, and Office of Blood Research and Review (OBRR) staff should be consulted when preparing the Chemistry, Manufacturing and Controls (CMC) section of the Biologic License Application (BLA). For questions concerning information to be submitted in the Establishment Description section, the staff of the Division of Manufacturing and Product Quality should be consulted.

[1] This guidance has been prepared by the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. 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 biological i*n vitro* diagnostic 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.

II. DEFINITIONS

In Vitro SUBSTANCES

In vitro substances are defined as any and all raw materials and intermediates used in the manufacture of the final *in vitro* product as defined in 21 CFR 820.3(c).

In Vitro PRODUCT

The *In Vitro* product is defined as the licensed product in its final form and all assembled supporting components.

PART 1 – CHEMISTRY, MANUFACTURING AND CONTROLS SECTION

I. *IN VITRO* SUBSTANCE

A. DESCRIPTION AND CHARACTERIZATION

1. Description

A clear description of each *in vitro* substance should be provided. These descriptions may include, but are not limited to, any of the following: chemical structure, primary and subunit structure, molecular weight, molecular formula, established USAN name, antibody class/subclass, etc., as appropriate.

2. Characterization

A description and the results of all the analytical testing performed to characterize the *in vitro* substances should be submitted (17, 19, 20, 22). Information from specific tests regarding identity, potency, specificity, purity, stability, consistency, etc. of the *in vitro* substances should be submitted.

a. Physicochemical Characterization

Examples of analyses for which information may be submitted include, but are not necessarily limited to the following.

- amino acid analysis
- amino- and carboxyl-terminal sequencing
- full amino acid sequencing
- peptide mapping/enzymatic mapping
- determination of disulfide linkage

- Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) (reduced and non-reduced)
- isoelectric focusing
- Conventional and High Pressure Liquid Chromatography (HPLC) e.g., reverse-phase, size exclusion, ion-exchange, etc.
- mass spectroscopy
- assays to detect substance-related proteins including deaminated, oxidized, clipped, and aggregated forms and other variants, e.g., amino acid substitutions, adducts/derivatives
- assays to detect residual non-specific host proteins, DNA, reagents
- immunochemical analyses
- assays to quantitate bioburden, endotoxin
- antibody neutralization
- hemagglutination
- hemagglutination inhibition
- antibody nitrogen level

Additional physicochemical characterization may be necessary for substances undergoing post-translational modifications, e.g., glycosylation, and for substances derivatized with other agents, including other proteins, enzymes, radionuclides, or chemicals. The information submitted should include the degree of derivatization or conjugation, the amount of unmodified substance, removal of free materials (e.g., enzymes, proteins radionuclides, etc.), and the stability of the modified substance as a result of the manufacturing process.

All test methods should be fully described, validated, and the results provided. The application should also include the actual data such as chromatograms, photographs of SDS-PAGE or agarose gel, spectra, etc.

b. Activity of the *in vitro* Substances

A description and results of all relevant *in vitro* (and where applicable *in vivo*) testing which is performed to show the potency, specificity, activity(ies) and acceptance criteria for each *in vitro* substance should be provided. (14 - 17, 21). The description and validation of each assay employed should include the methods and standards used, procedural steps, the inter- and intra-assay variability, linearity, and the acceptable limits of the assay.

B. MANUFACTURERS

1. Identification

The name(s), address(es), FDA registration number(s) and other pertinent organizational information for each manufacturer responsible for any portion of the manufacture or testing operations for the *in vitro* substance should be submitted. This may include contractors or other company subsidiaries serving as contractors, or other locations/sites owned and operated by the applicant. A brief description of the operations performed by each party and the responsibilities conferred upon each party by the applicant should be submitted.

2. Floor Diagram(s)

For each manufacturing location, a floor diagram that indicates the facility(ies) layout should be submitted. This diagram need not be a detailed engineering schematic or blueprint, but rather a simple drawing that depicts the relationship of the manufacturing areas, suites, or rooms to one another, and should indicate other uses made of adjacent areas that are not the subject of the application. This diagram should be sufficiently clear such that the reviewer may visualize the flow of the production of the *in vitro* substance and would be able to identify areas or room "proximities" that may be of concern for particular operations, e.g., segregation of pre- and post-viral inactivation material and operations. Room numbers or other unique identifiers should be provided, however the location of processing equipment within rooms and areas is not necessary. Reference can be made to manufacturing flow information presented in other areas of the submission and the General Information portion of the Establishment Description section.

3. Manufacture of Other Products

A comprehensive list of all additional substances to be manufactured or manipulated in the areas used for the product which is the subject of the application should be submitted. The applicant should indicate in which rooms the additional substances will be introduced and the manufacturing steps that will be performed. An explanation should be given as to whether additional substances will be introduced on a campaign basis or concurrently during production of the substance which is the subject of the application. Indication should also be given to additional substances that may share contact with equipment (dedicated vs. multi-use equipment should be delineated for each process step in this section or other appropriate sections of the application) used in the production. A brief description should be provided as to the type and developmental status of the additional substances.

4. Contamination Precautions

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

- air quality classification of room or area in which 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., provide if design represents an open or closed system or provides for a sterile or non-sterile operation;

- a description of the in-process controls performed to prevent or to identify contamination or cross contamination. The manipulation of more than one substance (e.g., cell lines, sera, antigens) in a single area or processed by non-dedicated equipment should be described and the measures used to ensure prevention of cross contamination should be discussed.

C. METHOD OF MANUFACTURE

1. Raw Materials and Substances

A list of all components used in the manufacture of the *in vitro* substance, and their qualifying tests and specifications, or reference to official compendia, should be submitted. For purchased raw materials, representative certificates of analysis from the supplier(s) and in-house acceptance testing results should be submitted. Note that process gases (e.g., air, carbon dioxide, etc.) and water are considered raw materials.

A list of qualifying tests, test results and acceptance criteria for all special reagents and materials used in the manufacture of the *in vitro* substance, e.g., culture media, diluents, dyes, reagents, buffers, sera, antibiotics, monoclonal antibodies, preservatives should be submitted. In some cases (e.g., a peptide or monoclonal antibody used in manufacture of the *in vitro* substance), a detailed description of preparation and characterization may be required (14 - 17).

A description of the tests and specifications for materials from an animal source that may potentially be contaminated with adventitious agents, e.g., mycoplasma, Bovine Spongiform Encephalophathy agent (BSE) for bovine derived products, and other adventitious agents of human and animal origin should be submitted.

Information (validation data) or certification supporting the freedom of substances from adventitious agents should be included in the submission.

In some cases an applicant may wish to purchase, rather than manufacture a licensed component of the final product. There are several possible regulatory approaches that might be used. Discussion of these approaches with CBER at the planning stage is recommended.

2. Flow Charts

A complete visual representation of the manufacturing process flow should be submitted. This flow chart should indicate for each step in production the equipment and materials used, the room or area where the operation is performed (may reference other parts of the application) and a complete list of the in-process controls and tests performed on the product at each step. This diagram should also include information (or be accompanied by a descriptive narrative) on the methods used to transfer the product between steps, i.e., sterile, steam-in-place (SIP) connection, sanitary connection, open transfers under laminar flow units, etc. Such transfers should be described for movement of product between equipment, areas/rooms, building sites, etc. References can be made to other sections of the application for more detailed process information.

3. Detailed Description

a. Animal Sources

Detailed guidance in this area may be obtained from the Draft Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use and the Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals.

Information submitted concerning animals used in manufacturing, such as mice used for ascites production, rabbits used for serum-antibody production, or transgenic animals, should include detailed information on the following:

- source and type of animals used (if transgenic, include the method of creation and the genetic stability)
- adventitious agent screening and the quarantine procedures used
- animal husbandry procedures
- veterinary oversight
- for bovine products specify geographic source and location of herd(s)
- immunogens used

  - immunogenicity
  - specificity
  - purity
  - sterility
  - stability
  - immunization type, dose and schedule
  - adjuvant if any
- Substance harvested
  - description of substance of interest
  - collection method, volume, receptacle, and schedule
  - description of processing steps and component(s) used
  - testing performed (titer/potency, affinity, specificity, sensitivity, bioburden, stability)
  - storage conditions
  - other characteristics unique to the substance, process or intended use.

b. Human Sources

The information submitted concerning the use of source material of human origin should include, but is not limited to, the following:

- donor suitability/acceptance criteria
- collection method, volume, and receptacle
- anticoagulants used
- description of component of interest
- component processing
- testing performed
  - infectious disease marker tests
  - titer (potency)
  - affinity
  - specificity
  - sensitivity
  - bioburden
  - stability
- purification and inactivation procedures
- storage conditions
- viral inactivation procedures
- immunization dose and schedule
- other characteristics unique to the substance, process or intended use.

c. Cellular Sources

The information submitted concerning the use of source material of cellular origin, e.g., in monoclonal antibody or recombinant DNA technology, should include, but is not limited to, the following:

- source and type of cells
- phenotype and genotype of cells
- characterization of the parent cell line
- cloning procedures
- immortilization procedures
- testing and monitoring procedures
- characterization of gene construct
- characterization of vector
- establishment, characterization, maintenance, and stability of cell banks
- cell culture procedures
- harvesting procedures
- purification and inactivation procedures
- downstream processing procedures
- other characteristics unique to the substance process or intended use.

Further information can also be found in the "Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use" dated August 1996.

d. Synthetic Sources

Information should be submitted concerning the use of materials from synthetic sources, e.g., 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".

D. PROCESS CONTROLS

1. In-process Controls

A description of the methods used for in-process controls, i.e., monitoring, testing, etc., used to assure that the functional requirement of the final product is met, e.g., integrity of solid-phase coatings, purity of enzyme labeled antibody/antigen conjugates, and potency, should be submitted.

2. Process Validation

A description and the results of the process validation studies should be submitted. If the manufacturing process was changed or scaled-up for commercial production and involved changes in the manufacturing steps, the re-evaluation of the process should be described, and the data and results provided. The description should include studies for the following processes which identify critical parameters to be used as in-process controls to ensure the success of routine production. Refer to the manufacturing flow diagram(s) as appropriate.

Validation studies should be submitted for the following:

- cell growth and harvesting processes
- purification processes
- inactivating or removing any infectious pathogens from substances used in the manufacturing process
- to demonstrate microbiologic control over those processes susceptible to microbiological contamination for substances labeled as sterile or where preservatives are used.
- solid-phase coating processes
- conjugation processes
- potency adjustments
- others as appropriate

E. REFERENCE STANDARDS/PANELS

1. Reference Standard

If an International Reference Standard (World Health Organization), CBER Reference Standard or compendial reference standard (U. S. Pharmacopoeia/National Formulary) is used, the citation for the standard and a certificate of analysis should be submitted. If no reference standard exists and the applicant establishes in-house, primary reference standards, a description of the characterization and specifications of the standards should be provided. The results of testing, such as amino acid analysis and biologic activity determination of the standard should be submitted. The Standard Operating Procedures (SOPs) to be used for qualifying a new reference standard should be included. Information should be provided on the stability of any reference standard.

2. In-house Reference Standard

In-house working reference standards should be used and the descriptions of the preparation, characterization, specifications, testing, substitutions, and results should be provided. The SOPs to be used for manufacture and qualification of a new in-house standard should be included. The data from the calibration of the in-house working reference standards should be compared against a primary reference standard and those results submitted.

F. SPECIFICATIONS/ANALYTICAL METHODS

1. *In vitro* Substance Specifications and Tests

Specifications and analytical methods used for release testing, shelf life determination and distribution conditions should be described in detail.

Specifications and tests for the *in vitro* substance which are used to assure its identity purity, strength and/or potency, specificity, and batch to batch consistency should be described in detail. (See applicable guidance documents in Appendix A). The analytical systems should be validated and the data should be provided for non-compendial methods to demonstrate the system suitability.

2. Impurities Profile

A discussion of the impurity profiles with supporting analytical data, should be provided. Profiles of variants of the protein *in vitro* substance (e.g., clipped, aggregated, deaminated, and oxidized forms), as well as non-product related impurities (e.g., process reagents and cell culture components), should be included.

G. CONTAINER/CLOSURE SYSTEM

A description of the in-process container and closure systems and their compatibility with the *in vitro* substance should be included (5). Detailed information concerning the supplier, address, and the results of compatibility, e.g., adsorption, leachables, biological tests, etc., should be included. Evidence of container and closure integrity for the duration of the proposed storage period should be provided.

H. STABILITY

A description of the storage conditions, SOPs, study protocols and results supporting the stability of the *in vitro* substance should be provided (3, 22, 24). This should include information on the stability of intermediate fluids or formulated bulk under specified holding or shipping conditions, as appropriate. Data from tests to monitor the biological activity and degradation products such as aggregated, deaminated, oxidized, and clipped forms should be included, as appropriate.

II. *IN VITRO* PRODUCT

A. MANUFACTURER

Include the name(s), and address(es) of all manufacturers involved in the manufacture and testing of the *in vitro* product, including contractors, and a description of the responsibility(ies) of each. A list of all other products (R&D, clinical or approved) made in the same rooms should be provided. If an investigational product formulation was different from that of the to-be-marketed finished product, clinical data to support equivalence of the two formulations should be provided, as appropriate.

B. COMPOSITION

A description of all components, including quantities, ratios or formulas used in the manufacture of the *in vitro* product in accordance with the "Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products" should be included. If an investigational product formulation was different from that of the to-be-marketed finished product, clinical data to support equivalence of the two formulations should be provided, as appropriate.

C. METHODS OF MANUFACTURING AND PACKAGING

A complete description of the manufacturing process flow for each formulated bulk should be provided. This discussion should include a description of non-sterile operations, as well as sterilization operations, aseptic processing procedures, vialing/filling, lyophilization, labeling, and packaging procedures. 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 other portions of the application) and a listing of the in-process controls and tests performed on the product at each step. This flow diagram or narrative should also include information on connections, sanitary connection, open transfers under laminar flow units, etc. Such transfers should be described for the movement of product between equipment, areas/rooms, building and sites. References can be made to other sections of the application for more detailed process information. Provide an assessment of baseline environmental conditions, a description of monitoring methods, specifications, and results obtained, and a description of methods of environmental control throughout all manufacturing areas used in production of the product.

D. SPECIFICATIONS AND TEST METHODS

This section should contain a description of all test methods and specifications used to assure the identity, purity, strength, and/or potency, specificity, and lot to lot consistency of the final finished product. The information submitted should include, but not be limited to:

- The sampling procedures for monitoring a lot of finished *in vitro* product.
- The validation data for system suitability for all non-compendial tests.
- The results of validation studies to ensure non-interference of special inactive ingredients, in USP compendial methods.
- Certificates of analysis and analytical results from in-house testing for at least three consecutive qualification lots of the *in vitro* substance should be provided.
- A description and results of all relevant *in vitro* (and where applicable *in vivo*) testing which is performed to show the potency, specificity, activity(ies) and acceptance criteria for each *in vitro* product, including
  - the methods and standards used,
  - procedural steps,
  - the inter- and intra-assay variability,
  - linearity,
  - the acceptable limits of the assay, and
  - bioburden testing.

E. CONTAINER/CLOSURE SYSTEM

A description of the container and closure systems, and their compatibility with the *in vitro* product should be provided. Detailed information concerning the supplier, address, and the results of compatibility and biological tests should be included. A device or drug master file (DMF) may be referenced for this information. Evidence of container and closure integrity should be provided for the duration of the proposed expiry period.

F. MICROBIOLOGY

If the product is 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." For additional guidance on other aspects of microbiologically controlled products, please refer to "Guideline for the Manufacture of In Vitro Diagnostic Products".

G. STABILITY

A description of the storage conditions, study protocols and results supporting the stability of the *in vitro* product should be provided. This should include information on the stability of intermediate fluids or formulated bulk under specified holding or shipping conditions, as appropriate. Stability data supporting the proposed shelf-life of the

reconstituted *in vitro* product and for all labeled dilutions should be provided. The validated results of all tests used to monitor performance characteristics, preservative effectiveness and the presence of degradation products such as aggregated, deaminated, oxidized, and clipped forms of the *in vitro* product should be provided (3, 11, 22, 24).

H. BATCH PRODUCTION RECORDS

A completed (executed) batch production record/device history record representative of the entire process of manufacturing and testing for the *in vitro* product should be submitted.

III. ENVIRONMENTAL ASSESSMENT

An environmental assessment should be prepared as outlined in 21 CFR Part 25. Provide a description of the action that is being considered and address all the components involved in the manufacture and disposal of the product. A statement of exemption under a Categorical Exclusion may be provided if applicable.

IV. METHOD VALIDATION

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

This section provides guidance on the content and format of information submitted in the Establishment Description section of a License Application for biological *in vitro* diagnostic products. The establishment description information submitted should be appropriate for the *in vitro* devices being manufactured and in accordance with 21 CFR Part 820 and other *in vitro* standards as appropriate. The information contained in this section need not be submitted for recombinant DNA derived *In Vitro* substances, synthetic peptide *In Vitro* substances, or monoclonal antibody *In Vitro* substances. For final In Vitro products that contain *In Vitro* substances in one or more of these three categories and other *In Vitro* substances, the information in this section should be submitted for the other *In Vitro* substances and all processes downstream of their incorporation into the final product.

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

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

B. HEATING, VENTILATING 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, nonviable particulate, and surface 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. 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.

1. Cleaning Procedures and Validation

a. 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.

b. 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.

2. 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 not be 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.

D. 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.

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. Guideline on Sterile Drug Products Produced by Aseptic Processing (1987)

3. Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics (1987)

4. Guideline for Submitting Samples and Analytical Data for Methods Validation (1987)

5. Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics (1987)

6. Guideline on General Principles of Process Validation (1987)

7. Guideline for Collection of Blood and Blood Products from Donors with Positive Tests for Infectious Disease Markers ("High Risk" Donors) (1989)

8. Guideline for Determination of Residual Moisture in Dried Biological Products (1990)

9. Draft Guideline for Reporting-ABR's-Adverse Reactions to Licensed Biological Products (1990)

10. Draft Guideline for Quality Assurance in Blood Establishments (1993)

11. Draft Recommended Methods for Evaluating Potency, Specificity, and Reactivity of Anti-Human Globulin (1992)

12. Draft Recommended Methods for Blood Grouping Reagents Evaluation (1992)

13. FDA's Policy Statement Concerning Cooperative Manufacturing Arrangements for Licensed Biologicals (1992)

14. Guideline for the Manufacture of In Vitro Diagnostic Products (1994)

15. Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances (1994)

Points to Consider

16. Draft Points to Consider in the Manufacture and Clinical Evaluation of In Vitro Tests to Detect Antibodies to the Human Immunodeficiency Virus, Type 1 (1989)

17. Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1997)

18. Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived From Transgenic Animals (1995)

19. Points to Consider-Characterization of Cell Line Used to Produce Biological Products (1993)

20. Points to Consider in the Design and Implementation of Field Trials for Blood Grouping Reagents and Anti-Human Globulins (1992)

21. Points to Consider in the Manufacture of *In Vitro* Monoclonal Antibody Products for Further Manufacture into Blood Grouping Reagents and Anti-Human Globulins (1992)

International Conference on Harmonization (ICH) Guidelines

22. Stability Testing of New Drug Substances and Products (9/22/94)

23. Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products (2/23/96)

24. Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products (7/10/96)