

## **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**

**Center for Biologics Evaluation and Research (CBER)  
Center for Drug Evaluation and Research (CDER)  
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## GUIDANCE FOR INDUSTRY<sup>1</sup>

### 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

#### I. INTRODUCTION

In the Federal Register of May 14, 1996, the Food and Drug Administration published the final rule "Elimination of the Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products". Under this rule manufacturers of therapeutic recombinant DNA-derived products and/or monoclonal antibody products for in vivo use are no longer required to submit an Establishment License Application and may use the interim FDA Form 3439. This document provides guidance on the content and format of the Chemistry, Manufacturing, and Controls (CMC) section of a Biologics License Application for therapeutic recombinant DNA-derived products and monoclonal antibody products for in vivo use.

#### II. DRUG SUBSTANCE

The drug substance is defined as the unformulated active substance which may be subsequently formulated with excipients to produce the drug product.

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<sup>1</sup>This guidance is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgement of employees of the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER), at this time. This statement does not necessarily represent the formal position of CBER or CDER and does not bind or otherwise obligate CBER or CDER to the views expressed. For further information about this guidance, contact Neil Goldman, Ph.D., Associate Director for Research, Center for Biologics Evaluation and Research, 4401 Rockville Pike, Rockville, MD 20852 (Phone: 301-827-0375; Fax: 301-827-0440) or Yuan-Yuan Chiu, Ph.D., Supervisory Chemist, Biotechnology Subcommittee, Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-443-3510; Fax: 301-443-9282).

## **A. Description and Characterization**

### **1. Description**

A clear description of the drug substance should be provided. This description may include, but not be limited to, any of the following: chemical structure, primary and subunit structure, molecular weight, molecular formula, established USAN name, antibody class/subclass (if appropriate), etc.

### **2. Characterization / Proof of Structure**

#### **a. Physicochemical Characterization of Reference Standard and Qualifying Lots:**

A description and the results of all the analytical testing performed on the manufacturer's reference standard lot and qualifying lots to characterize the drug substance should be included (See references 7, 8, 10). Information from specific tests regarding identity, purity, stability and consistency of manufacture of the drug substance should be provided. Examples of analyses for which information may be submitted include, but are not necessarily limited to the following:

- amino acid analysis
- amino acid sequencing, entire sequence or amino- and carboxy-terminal sequences
- peptide 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 product-related proteins including deamidated, oxidized, cleaved, and aggregated forms and other variants e.g., amino acid substitutions, adducts/derivatives.
- assays to detect residual host proteins, DNA, reagents
- immunochemical analyses
- assays to quantitate bioburden, endotoxin

Additional physicochemical characterization may be required for products undergoing post-translational modifications, for example, glycosylation, sulfation, phosphorylation, or formylation.

Additional physicochemical characterization may also be required for products derivatized with other agents, including other proteins, toxins, drugs, radionuclides, or chemicals. The information submitted should include the degree of derivatization or conjugation, the amount of unmodified product, removal of free materials (e.g., toxins, radionuclides, linkers, etc.), and the stability of the modified product.

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

#### **b. Biological Activity**

A description and results of all relevant in vivo and in vitro biological testing performed on the manufacturer's reference standard lot to show the potency and activity(ies) of the drug substance should be provided. Results of relevant testing performed on lots other than the reference standard lot, that might have been used in establishing the biological activity of the



product, should also be included. (See references 7 - 10, 12) The description and validation of the bioassays should include the methods and standards used, the inter- and intra-assay variability, and the acceptable limits of the assay.

## **B. Manufacturer(S)**

### **1. Identification**

The application should include the name(s), address(es), FDA registration number, and other pertinent organizational information for each manufacturer performing any portion of the manufacture or testing operations for the drug substance. This may include contractors or company subsidiaries serving as contractors, or other locations/sites owned and operated by the applicant. A brief description of the operations performed at each location, the responsibilities conferred upon each party by the applicant and a description of how the applicant will ensure that each party fulfills their responsibilities should be submitted.

### **2. Floor Diagram(s)**

For each manufacturing location, a floor diagram should be included that indicates the general facility(ies) layout. This diagram need not be a detailed engineering schematic or blueprint, but rather a simple drawing that depicts the relationship of the subject 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 drug 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, segregation of animal facilities, etc. Room numbers or other unique identifiers should be provided, however it is not necessary to include the location of processing equipment within rooms and areas. Reference can be made to manufacturing flow information presented in response to section II. C. 2. of this guidance.

### **3. Other Products**

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

### **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 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, eg. 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(S) of Manufacture**

### **1. Raw Materials and Reagents**

A list of all components used in the manufacture of the drug substance, and their tests and specifications or reference to official compendia should be provided. For purchased raw materials representative certificates of analysis from the supplier(s) and/or manufacturer's acceptance criteria should be included in the submission. Process gases (e.g., air, carbon dioxide) and water are considered raw materials.

A list with tests and specifications of all special reagents and materials used in the manufacture of the drug substance, e.g., culture media, buffers, sera, antibiotics, monoclonal antibodies, preservatives, should be submitted. In cases where an ancillary biological product is used in the manufacture of the drug substance (e.g., a monoclonal antibody used in affinity chromatography), a detailed description of the preparation and characterization of the reagent should be submitted (Reference 7, 10).

A description of the tests and specifications for materials of human or animal source that may potentially be contaminated with adventitious agents, e.g., mycoplasma, Bovine Spongiform Encephalopathy (BSE) agent for bovine derived products, and other adventitious agents of human and animal origin should be submitted. Validation data or certification supporting the freedom of reagents from adventitious agents should be included in the submission.

## **2. Flow Charts**

A complete visual representation of the manufacturing process flow should be provided. This flow chart should indicate the step in production, the equipment and materials used, the room or area where the operation is performed (may reference the simple diagram in II. B. 2.) 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, buildings and sites. Manufacturing steps which are computer controlled should be identified. References can be made to other sections of the application for more detailed process information.

## **3. Detailed Description**

### **a. Animal Sources**

The information submitted concerning animals used in production, such as mice used for ascites or transgenic animals, should include detailed descriptions of the following:

- source of animals;
- method of creating and the genetic stability of transgenic animals;
- adventitious agent screening and quarantine procedures used to assure animals are appropriate for use in manufacturing;
- animal husbandry procedures, and;
- veterinary oversight.

More detailed guidance in these areas may be obtained from the "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."

**b. Cellular Sources**

**i. Cell Substrate / Host Cell / Expression Vector System**

**A. Recombinant DNA Products including rDNA-Derived Monoclonal Antibodies.**

The submission should include a detailed description of the host cell and expression vector system and their preparation as delineated below: (See References 9, 10, 12)

**I. 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.

**II. 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.

### **III. 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.

### **IV. 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.

v. **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.



**B. Monoclonal Antibodies.**

A detailed description of the development of the monoclonal antibody should be provided including characterization of the parent cells, donor history for human cells, immunogen, immortalization procedures, screening, and cell cloning procedures. (See Reference 7, 9)

**ii. Cell Seed Lot System**

**A. Master Cell Bank (MCB)**

A detailed description of the preparation and testing of the MCB, as outlined below and in the ICH guideline "Analysis of the Expression Construct in Cells used for Production of R-DNA Derived Protein Products", should be submitted.

The MCB should be described in detail, including methods, reagents and media used, date of creation, quantity of the cell bank, in-process controls, and storage conditions. The results of the characterization of the MCB for identity and purity using appropriate phenotypic markers such as morphology, auxotrophy, isoenzyme, etc. should be included. Restriction enzyme analysis and DNA sequencing data supporting the integrity of the introduced genetic sequence and data supporting the stability of both the host cell and final gene construct during storage should also be submitted. For bacterial cells, the results of tests for contamination with both lytic and lysogenic bacteriophages and

non-host microorganism(s) should be included.

The testing of the MCB for endogenous and adventitious agents (e.g. Murine retroviruses, Epstein-Barr virus, mycoplasma, bacteria, fungi, other viruses and/or virus-like particle), as appropriate, as outlined in "Points to Consider in Characterization of Cell Lines used to Produce Biological Products", 1993, and "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use" should be described. If new Master Cell Banks are to be generated by transfer of final DNA construct to host cells or by expansion of an existing MCB or Working Cell Bank (WCB), then acceptance criteria for both the new cell bank and the drug substance(s) produced by the new bank should be described. In particular, documentation of the fidelity of the introduced nucleotide sequence in the new MCB and restriction mapping analysis should be submitted.

**B. Working Cell Bank**

A detailed description of the preparation and testing of the WCB such as those outlined in the applicable guidance documents (References 7, 9, 10, 12) should be submitted.

The production of the Working Cell Bank should be described in detail, including methods, reagents and media used, date of creation, quantity of the cell

bank, number of cell doublings from the MCB and storage conditions. If there is no MCB, the results of the characterization of the WCB should be provided in the format detailed for the MCB (Section II. C. 3. b. ii.).

**c. End of Production Cells (EPC)**

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" and "Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use."

**iii. Cell Growth and Harvesting**

A detailed description of the process of inoculation, cell growth and harvesting should be submitted. The composition of the medium, equipment preparation and sterilization, as well as fermentation medium sterilization, should be described. For all stages

of any fermentation process the procedures which prevent contamination with adventitious agents should be described.

The stages of cell growth should be described in detail including the selection of inoculum, scale-up for propagation, and established and proposed (if different) production batch size. All operating conditions and in-process controls should also be described and appropriate ranges for operating and control parameters, such as fermentation time, cell doubling time, cell culture purity, cell viability, pH, CO<sub>2</sub>, etc., established. If induction is required for production of protein, detailed information including induction conditions and controls employed should also be described.

The submission should include the process used to inactivate cells utilized in the production of a drug substance prior to their release into the environment. For cell lines meeting the criteria of Good Large Scale Practice (GLSP) organisms (July 18, 1991 FR notice, Vol. 56, no 138, p. 33174), which do not require inactivation prior to release into the environment, the information supporting their qualification as GLSP organisms should be provided. A description of the procedures used, in the event of a contamination, to inactivate a GLSP culture prior to release should be included.

If the culture supernatant or cell pellet is stored prior to processing, data supporting its stability during storage should be provided.

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. Purification and Downstream Processing**

A detailed description of the purification and downstream processing, including a rationale for the chosen methods, and the precautions taken to assure containment and prevention of contamination or cross contamination should be provided.

In-process bioburden and endotoxin limits should be specified where appropriate. Any reprocessing using a validated reprocessing method and the conditions for batch eligibility should be described.

If applicable, indication (or reference to II. B. 2. ) should be made as to the multi-use nature of areas and equipment (e.g. campaigning vs. concurrent manufacture; dedicated vs. shared equipment) used for these procedures. A brief description of the controls employed to ensure segregation and prevent cross contamination, or reference to another section containing this information, should be provided.

**4. Batch Records**

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

## **D. Process Controls**

### **1. In-Process Controls**

A description of the methods used for in-process controls, e.g., those involved in fermentation, harvesting and downstream processing, should be provided.

### **2. Process Validation**

A description and documentation of the validation studies should be provided. If the process was changed or scaled up for commercial production and involved changes in the fermentation steps, the re-validation of cell line stability during growth should be described, as in the previous section, and the data and results provided.

#### **a. Validation Studies for the Cell Growth and Harvesting Process.**

A description and documentation of the validation studies which identify critical parameters to be used as in-process controls, to ensure the success of routine production should be submitted. Reference may be made to the flow diagram(s) as appropriate.

#### **b. Validation Studies for the Purification Process.**

A description and documentation of the validation of the purification process to demonstrate adequate removal of extraneous substances such as chemicals used for purification, column contaminants, endotoxin, antibiotics, residual host proteins, DNA, and viruses, where appropriate, should be provided. (See references 4, 7 - 10)

**c. Microbiology.**

A description and documentation of the validation studies for any processes used for media sterilization, 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."

**E. Reference Standard(s)**

**1. Primary Reference Standard**

If an international reference standard (WHO, NIBSC) or compendial reference standard (USP) is used, submit the citation for the standard and a certificate of analysis. If no biological potency or chemical reference standard exists, and the applicants establish their own primary reference standard, a description of the characterization, and specifications of the standard should be provided. Submit the results of testing, such as physicochemical and biologic activity determinations, of the standard and provide a certificate of analysis. The Standard Operating Procedures (SOPs) to be used for qualifying a new reference standard should be included. Information should also be provided on the stability of any reference standard.

**2. Working Reference Standard (if used).**

If an in-house working reference standard is used, a description of the preparation, characterization, specifications, testing and results should be provided. The data from the calibration of the in-house working reference standards against a primary reference standard should also be submitted.

**F. Specifications / Analytical Methods**

**1. Drug Substance Specifications and Tests.**

- a. Specifications and analytical methods used for release testing, shelf life and distribution should be described.**

Specifications and tests for the drug substance sufficient to assure its identity, purity, strength and/or potency, as well as lot-to-lot consistency should be submitted. (See references 3, 4, 7 - 11, 13) Validation of the analytical systems and the data should be provided for non-compendial methods to demonstrate the system suitability.

- b. Certificates of Analysis and Analytical Results**

Certificates of analysis and analytical results for at least three consecutive qualification lots of the drug substance should be submitted.

**2. Impurities Profile.**

A discussion of the impurities profiles, with supporting analytical data, should be provided. Profiles of variants of the protein drug substance (e.g., cleaved, aggregated, deamidated, oxidized forms, etc.), as well as non-product related impurities (e.g., process reagents and cell culture components), should be included.

**G. Container/Closure System(S)**

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.

#### **H. Drug Substance Stability**

A description of the storage conditions, study protocols and results supporting the stability of the drug substance should be submitted in this section. (Refer to ICH document "Stability Testing of Biotechnological/Biological Products" or other FDA documents such as "Guideline for Submitting Documentation for the Stability of Human Drug and Biologics" for specific information.)

Data from tests to monitor the biological activity and degradation products such as aggregated, deamidated, oxidized, and cleaved forms should be included, as appropriate. Data supporting any proposed storage of intermediate(s) should also be provided.

### **III. DRUG PRODUCT**

#### **A. Composition, including components.**

A tabulated list of all components with their unit dose and batch quantities for the drug product or diluent in accordance with the "Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products" should be submitted. The composition of all ancillary products that might be included in the final product should be included.

#### **B. Specifications & Methods for Drug Product Ingredients**

##### **1. Drug Substances Including All Active Ingredients and Ancillary Components.**

This section should contain a description of tests and specifications for all active ingredients, if not specified in the Drug Substance section. The specifications for all ancillary products that are included in this product should be provided.

## **2. Excipients:**

Information on all excipients including process gases and water should be included.

### **a. Compendial Excipient(s).**

A list of compendial excipients and the citations for each should be submitted.

### **b. Non-Compendial Excipient(s).**

Tests and specifications should be described. For a novel excipient, the description should include its preparation, characterization, and controls. For inactive ingredients of human or animal origin, certification, results of testing or other procedures, or validation data demonstrating their freedom from adventitious agents should be provided.

## **C. Manufacturer(s)**

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 II. B. 3. of this document for detailed guidance.

## **D. Methods of Manufacture and Packaging**

A complete description of the manufacturing process flow of the formulated bulk and finished drug product should be provided. This discussion should include a description of sterilization operations, aseptic processing procedures, lyophilization, 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 the simple diagram in II. B. 2.) 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 the methods of transfer of the product between steps, i.e. Sterile, SIP connection, sanitary connection, open transfers under laminar flow units, etc. Such transfers should be described for movement of product between equipment, areas/rooms, buildings and sites. References can be made to other sections of the application for more detailed process information.

## **E. Specifications & Test Methods for Drug Product**

### **1. Sampling Procedures**

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

### **2. Specifications & 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.

The validation data for system stability for all non-compendial tests should be provided. If compendial methods have to be validated to ensure non-interference of special inactive ingredients, the results of those validation studies should be submitted.

## **F. Container/Closure System(s)**

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.

#### **G. 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."

#### **H. Drug Product Stability**

A description of the storage conditions, study protocols and results supporting the stability of the drug 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. For products administered through pumps or other such delivery devices, data on the stability of the drug product in the delivery system should be provided. Stability data supporting the proposed shelf-life of the reconstituted drug product and for all labeled dilutions should be included. The results of all tests used to monitor biological activity and the presence of degradation products such as aggregated, deamidated, oxidized, cleaved, etc. forms of the drug substance should also be included. (See references 3, 7 - 13)

### **IV. INVESTIGATIONAL PRODUCT/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. 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 (See reference 6).

### **V. ENVIRONMENTAL ASSESSMENT**

An environmental assessment should be prepared as outlined in 21 CFR Part 25. This submission 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. A statement of exemption under a Categorical Exclusion may be provided if applicable.

## **VI. METHOD VALIDATION**

Provide information as described in the "Guideline for Submitting Samples and Analytical Data for Methods Validation."

## **VII. REFERENCES**

### **Guidelines**

- 1 Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
- 2 Guideline on Sterile Drug Products Produced By Aseptic Processing.
- 3 Guideline for Submitting Documentation for the stability of Human Drugs and Biologics
- 4 Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products
- 5 Guideline for Submitting Samples and Analytical Data for Methods Validation
- 6 FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products

### **Points To Consider**

- 7 Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1994)
- 8 Points to Consider in the Manufacture and Testing of

Therapeutic Products for Human Use Derived from  
Transgenic Animals, 8/22/95

- 9 Points to Consider - Characterization of Cell Line  
used to Produce Biological Products, 7/12/93
- 10 Points to Consider in the Production and Testing of  
New Drugs and Biologics Produced by Recombinant DNA  
Technology, 4/10/85

**International Conference on Harmonization (ICH) Guidelines**

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- 12 Analysis of the Expression Construct in Cells used for  
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