

Guidance for Industry

For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma- Derived Biological Products, Animal Plasma or Serum-Derived Products

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
February 1999**

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Guidance for Industry:¹

For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Products, Animal Plasma or Serum-Derived Products

GENERAL INFORMATION

I. BACKGROUND

In the *Federal Register* of July 8, 1997 (62 FR 36558), the Food and Drug Administration (FDA) announced the availability of the revised Form FDA 356h, Biologics License Application (BLA) entitled “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) section and the Establishment Description section of a Biologics License Application for a Human Plasma-Derived Biological Product, Animal Plasma or Serum-Derived Product. For these products, FDA is now implementing the BLA (revised Form FDA 356h) and will accept that application, instead of two separate license application submissions, the product license application (PLA) and the establishment license application (ELA).

This document supersedes the draft guidance entitled “Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Products or Animal Plasma or Serum-Derived Products” that was announced in the *Federal Register* of January 21, 1998 (63 FR 3145).

II. DEFINITIONS

Plasma Proteins

The liquid portion of blood contains many dissolved components, primarily proteins which are important in the humoral immune systems and the coagulation system. Immune proteins are predominantly immunoglobulins, antibodies, which react specifically with antigens. Coagulation proteins contribute to the series of enzyme-substrate reactions and platelet function which are responsible for maintaining hemostasis.

¹ This document represents FDA’s current thinking on the content and format of the Chemistry, Manufacturing and Controls and Establishment Description information for human plasma-derived, biological products, animal plasma or serum-derived products. 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.

Human Plasma-Derived Biological Product

Many important therapeutic products are purified from human plasma. Plasma is the liquid portion of blood and is usually separated from the formed components in single units at collection. Plasma contains anticoagulants so that the coagulation proteins are not activated and the collected blood does not clot. Collection is performed by apheresis or by centrifugation of whole blood. The units of plasma are usually pooled into large batches for separation into the various therapeutic components. Some of these components are proteins circulating in normal blood. In other cases, the plasma is screened to identify units which may have high amounts (titer) of a specific component, e.g., immunoglobulins to rabies virus. These high titered units are then pooled for fractionation.

Animal Plasma, Serum-Derived Product

Historically, the immunization of animals for the collection of specific immune plasma or serum is a method that has been very effective and safe. The serum as a source for the biological product is different than plasma in that the blood is allowed to clot and most of the coagulation proteins are removed.

Fractionation

The process of separating specific biological function from the mixture of plasma or serum proteins is referred to as fractionation. Plasma is separated into different “fractions” using various chemical and physical methods to allow the concentration of the desired activity and removal of unwanted activity and contaminants.

Virus Clearance

Many manufacturing steps have been demonstrated to remove or inactivate particular viruses. This demonstration is performed in the laboratory to avoid contamination of manufacturing facilities and to properly contain the agents that are used in the validation studies. A number of principles may be used to demonstrate expected removal or inactivation of infectious virus. One of these is the use of actual manufacturing materials in an appropriate reproduction of a particular manufacturing step on a smaller scale. Where particular agents of interest or testing methods are unavailable, model viruses which are similar in specific characteristics may be used. Because of limitations in the attainable titer of particular viruses, individual manufacturing steps, rather than the entire manufacturing process are usually evaluated; however, more than one step might be evaluated in a single experiment. A manufacturing scheme may include steps which are intended to specifically address removal and steps which specifically address inactivation.

PART 1 – CHEMISTRY, MANUFACTURING AND CONTROLS SECTION

I. INTRODUCTION

The starting materials for human plasma-derived products are known to be capable of transmitting infectious disease and many of the infectious agents of primary concern have been identified. The approach to viral safety of plasma-derived materials incorporates donor screening, testing for agent markers in source material, validation of removal or inactivation of known and model viruses, lot release testing where appropriate, and effective surveillance following marketing. All of these areas should be addressed in designing and validating the manufacturing process. All manufacturing methods and validations of the process should be described in the CMC section of the Biologics License Application.

II. BIOLOGICAL SUBSTANCE/PRODUCT

Production of a human plasma-derived, animal plasma or serum-derived biological component requires a complex series of manufacturing steps. The consistent production of these materials relies on validation of the processes involved and on the control of the validated processes. Each manufacturing step begins with the product from the preceding step. The routine control of manufacturing relies on correct raw materials, in-process testing, and exact adherence to manufacturing procedures as specified and validated. Thus, the evaluation of a manufacturing process involves all of these factors. In order for this evaluation to be complete, all components of the process should be completely validated and described.

A. Description and Characterization

1. Description
 - a. Names: This section should contain a list of the names of the product. This may include, but is not limited to, any of the following: name(s) and, as appropriate and available, the established (proper or generic) and proprietary (brand) names or synonyms.
 - b. Active Biological Component: A clear description of the biological substance should be provided. This description may include applicable information that briefly and succinctly characterizes the biological substance.
2. Characterization

This section should contain specific tests that will provide information regarding identity, stability and consistency of manufacture for the biological drug substance. All test methods should be fully described and data provided.

 - a. Physicochemical Characterization (Biological Specifications)

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

- Potency Assays,
 - Chromatographic Assays,
 - Electrophoresis, e.g., Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE),
 - Immunoblot Analysis,
 - Fluorescence Activated Cell Sorter (FACS) Analysis,
 - Enzyme-Linked Immunosorbent Assay (ELISA).
- b. Biological Activity Potency
Biological testing performed on the manufacturer's reference (standard lot or test lot) to determine potency/biological activity of the product should be described. This description of the potency assay should include the methods and standards used and the variability and acceptable limits of the assay.
- c. Statistical Analysis/Data Validating Methods
Results of statistical analysis/data validating assay methods and procedures ensuring accurate results and/or potency levels should be provided.

B. Manufacturer(s)

1. Identification
This section should include the name(s), address(es), zip code(s), telephone number(s), FDA registration number, and other pertinent organizational information for each manufacturer, storage, testing, and labeling facility responsible for any portion of the manufacture or testing operations for the biological product. This may include independent contractors, animal care facilities or other company subsidiaries serving as contractors, or other locations/sites owned, operated and contracted 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. The steps taken by the applicant to ensure that each party fulfills its responsibilities should also be described.
2. Floor Diagram(s)
For each manufacturing/testing/storage location, a floor diagram should be included that indicates the general facility(ies) layout. The 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 the adjacent areas that are not the subject of the application. This diagram should be sufficiently clear so that the reviewer may visualize the flow of production of the biological

substance and would be able to identify areas or room “proximities” that may be of concern for particular operations (e.g., segregation of 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 charts described in Part 1, Section II.C.2. of this document.

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. A brief description should be provided as to the type and developmental status (including pre-clinical and investigational) of the additional products. 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).

4. Contamination

For all manufacturing areas, 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 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 product in a single area, or the use of any piece of equipment for more than one product, should be indicated and measures to ensure prevention of cross-contamination should be discussed.

C. Methods of Manufacturing and Packaging

This section should be completed for each biological substance described in Part 1 Section II. A detailed description of the manufacturing and controls should be provided to demonstrate proper quality control or prevention of possible contamination with adventitious agents. The inclusion of a list of all relevant Standard Operating Procedures (SOPs) is recommended.

1. Starting Materials

Materials used in the collection and processing of the biological substance should be fully described. This description should include a list of starting materials, reagents, and auxiliary materials with specifications or statements of the quality of each. Any alternative methods or variations in the manufacturing process should be included with an explanation of the circumstances under which they would be used.

- a. For purchased raw materials, representative certificates of analysis from the suppliers or the manufacturer's own acceptance testing results should be submitted. This should include information on expiration dating, and frequency limits of re-testing if raw material is not used within a specified time.
- b. The tests and specifications for materials of animal source that may potentially be contaminated with adventitious agents, e.g., Bovine Spongiform Encephalopathy (BSE) for fetal bovine serum, and viruses in products of human and animal origin should be fully described. Information or certification supporting the freedom of reagents from adventitious agents should be included in the submission.
- c. The plasma source should be described and whether it was obtained as recovered, source or under short supply agreements. A description of the type of shipping and the storage temperature, and the disposal of rejected plasma should be included.
- d. A list of tests and specifications for all special reagents and materials used in the manufacture of the drug substance, e.g., buffers, sera, antibiotics, monoclonal antibodies, and preservatives should be included. In some cases (e.g., a monoclonal antibody used in manufacture of the biologic) a detailed description of their preparation and characterization should be provided. If human tissues are used for absorption or adsorption, testing for donor suitability should be described.
- e. Many plasma fractionation facilities receive intermediate products from other manufacturers. A description of the specifications for the intermediate product should be provided along with data supporting its stability during storage and shipping.
- f. The receipt or manipulation of materials to be used for different products in a single area or piece of equipment should be indicated and

measures to ensure prevention of cross-contamination should be discussed (e.g., some fractionation facilities may process plasma collected outside the United States for use outside the U.S.)

2. Flow Charts

In this section, a complete visual representation of the manufacturing process flow should be provided. 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. 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 and procedures should be fully described. The following should be addressed in detail.
 - How animals are entered into production;
 - Source of animals;
 - Immunization methods;
 - Animal husbandry procedures including;
 - Adventitious agent screening and quarantine procedures;
 - Veterinary oversight;
 - Bleeding protocols;
 - A description of the areas and environmental conditions for manipulating production animals;
 - A description of any special equipment and cleaning methods; and
 - A description and illustration of the physical separation between animal facilities and other manufacturing areas and personnel flow between these areas. Segregation procedures for multi-product areas should be described. Reference may be made to other sections of the submission as applicable.
- b. A detailed description of the fractionation, formulation, and purification should be provided. This should include a rationale for the chosen methods, and the precautions taken to assure containment and prevention of contamination or cross-contamination. In-process bioburden and endotoxin limits should be specified where appropriate. Any reprocessing or related method should be fully validated and

described. The allowable conditions for reprocessing of all or part of any batch should be described. Critical operations during which product or product contact surfaces are exposed to the environment should be described. If barrier isolator systems are used, a description of the system and the conditions of its use should be provided. Information and data on drug product filtration should be provided.

4. Batch Records: A completed batch record of the process of production of the biologic product should be included.

D. Process Controls

1. A description of the control checks performed at various stages of the manufacture, processing, and packaging of the biological substance should be submitted. The description should include the specifications and tests for any intermediate steps with justification, as needed, for their use. Yield calculations at each major step in manufacturing should be performed.
2. A description of in-process and *final* controls, including analytical tests and appropriate data to support the specifications should be submitted.
3. Any additional information regarding the processing or possible reprocessing of the final product should be submitted. This should include the rationale for the reprocessing, and a description of the circumstances under which reprocessing would be allowed as well as any validation data to indicate how reprocessing would affect the product.
4. Validation data should be provided for a number of processes.
 - a. A description of the validation studies which identify, and establish acceptable limits for critical parameters to be used as in-process controls, to assure the success of routine production. Reference may be made to flow charts or diagrams as appropriate.
 - b. Validation studies for the purification process; a description of the validation of the purification process to demonstrate adequate removal of extraneous substances such as chemicals used in the purification, column contaminants, endotoxin, antibiotics, residual plasma proteins, non-viable particulates, and viruses should be provided.
5. Microbiology
 - a. If the product is intended to be sterile, information on all sterilization and aseptic processes (e.g., formulation through filling

and sealing) 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” and “Guideline on Sterile Drug Products Produced by Aseptic Processing.”

- b. A description of the validation studies for any processes used for inactivation of waste for release into the environment should be provided.

E. Reference Standards

1. Primary reference standard
 - a. If an international standard (World Health Organization, National Institute of Biological Standards and Control) or compendial reference standard (United States Pharmacopoeia) is to be used, the citation for the standard and a certificate of analysis should be submitted.
 - b. If there is no reference standard and the applicant establishes its own, a description of the preparation, characterization, and specifications of the standard should be provided. The results of standard testing, such as biologic activity determination, should be submitted, and a certificate of analysis should be provided. The SOPs to be used for qualifying a new reference standard should be included. Stability data on the standard should also be provided.
 - c. A description of the storage conditions and control procedures should be provided.
2. Working reference standard

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. Biological drug product specifications and tests
 - a. Specifications and analytical methods used for release testing, expiration dating, acceptable regulatory specifications and tests for the product, sufficient to assure its identity, purity, strength, or potency and lot-to-lot consistency should be submitted. Validation of the analytical systems and the data should be provided for non-compendial methods to demonstrate the system suitability.
 - b. Lot release protocols, including specification ranges of representative lots of the product should be provided.

Specifications may include, but not be limited to, biochemical purity, safety, appearance, pH, residual moisture, excipients, endotoxins, and sterility.

- c. A description of all materials packaged with the biological products such as diluent or syringe, should be described and their appropriate FDA designation if approved separately.
 - d. Methods and standards of acceptance, including the sampling plan and the accuracy and precision of the analytical methods should be sufficiently detailed to permit duplication and verification.
2. Excipients
 - a. A list of compendial excipients and citations for each should be submitted.
 - b. For non-compendial excipients, tests and specifications should be described. For novel excipients, the preparation, characterization, and controls should be described. For inactive ingredients of human or animal origin, provide certification or results of testing or other procedures demonstrating their freedom from adventitious agents.
 3. Impurities Profile

A discussion of the impurity profiles, with supporting analytical data, should be provided. Profiles of variants of the protein including proteolytic break down products, aggregated forms, chemically modified forms which are all product related substances should be determined. Non-product related impurities, e.g., process reagents, should be identified where possible. In addition, other active plasma components that may be present should be identified. Specifications should be set for each of these categories of impurity.

G. Container Closure System/Shipping Containers

A description of the container and closure system, and its compatibility with the biological substance should be submitted. This should include detailed information concerning the supplier, address, and the results of compatibility, toxicity and biological tests. Evidence of container and closure integrity should be provided. If the container or closure manufacturer has a Master File with the FDA, a letter authorizing the applicant to cross-reference that file should be submitted.

H. Stability

1. A description of the storage conditions, study protocols and results supporting the stability of the biological product and any intermediates that are stored should be submitted.

2. Data from tests to monitor the biological activity or degradation products, if any, should be included as appropriate.
3. Measures taken to assure that acceptable conditions are maintained during transport should be described, and the validation that the product is stable under those conditions should be submitted.
4. A complete description of, and data derived from, studies of the suitability of the biological product, including information showing the stability of the analytical method(s) used, should be submitted. This should include descriptions of any additional stability studies underway or contemplated. Stability data should be submitted for the biological product as packaged in the container in which it is to be marketed. The expiration dating period proposed to be shown on the label should be stated and the date of manufacture should be described, as well as how it is assigned. The validation demonstrating that the product is stable under the conditions in which it is used should be submitted.

III. INVESTIGATIONAL PRODUCT/FORMULATION

A discussion of any differences in formulation, manufacturing process, or site between the clinical trials materials and commercial production batches of biological drug substance/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, as 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.

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. Refer to “Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications.”

V. 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

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 the establishment description section of a Biologics License Application for products derived from human plasma, animal serum or animal plasma.

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. 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. 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. 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. 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. 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. 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. 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. Lyophilization

A validation summary for lyophilization of the drug substance/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.

E. 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

Guidelines

1. Interpretive Guidelines for the Additional Standards for Source Plasma (Human) Standards (10/73)
2. Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics (2/87)
3. Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics (2/87)
4. Guideline on Sterile Drug Products Produced by Aseptic Processing (6/87)
5. Guideline on General Principles of Process Validation (5/87)
6. Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices (12/87)
7. Guidelines for Reviewing Amendments to Include Plasmapheresis of Hemophiliacs (7/76)
8. Guideline for the Determination of Residual Moisture in Dried Biological Products (1/90)
9. Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (11/94)
10. Guideline for Submitting Samples and Analytical Data for Methods Validation (2/87)
11. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (7/98)
12. FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology Derived Products (4/96)

Points to Consider

1. Points to Consider in the Production and Testing of New Drugs and Biologics Produced by Recombinant DNA Technology (4/85)
2. Points to Consider in the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals (1995)

International Conference on Harmonization (ICH) Guidelines

1. Stability Testing of New Drug Substances and Products (9/94)
2. Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (7/96)
3. Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (5/96)

Other Publications

1. Revised Recommended Methods for Evaluating Potency, Specificity, and Reactivity for Anti-Human Globulin (5/92)
2. FDA's Policy Statement Concerning Cooperative "Manufacturing Arrangements for Licensed Biologics" (11/92)
3. Office of Establishment Licensing and Product Surveillance Advertising and Promotional Labeling Staff Revised Procedural Guide (8/94)