Guidance for Industry

On the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for an Allergenic Extract or Allergen Patch Test

Additional copies are available from:
Office of Communication, Training and
Manufacturers Assistance (HFM-40)
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 1-800-835-4709 or 301-827-1800

(Internet) http://www.fda.gov/cber/guidelines.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
April 1999

Table of Contents

Note: page numbering may vary for documents distributed electronically.

Guidance for Industry:[1]

On the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for an Allergenic Extract or Allergen Patch Test

GENERAL INFORMATION

I. BACKGROUND

In the Federal Register of July 8, 1997, the Food and Drug Administration announced the availability of Revised Form FDA 356h "Application to Market a New Drug, Biologic, or an Antibiotic for Human Use." This document provides guidance on the content and format of the Chemistry, Manufacturing, and Controls (CMC) section of a Biologics License Application for an Allergenic Extract or Allergen Patch Test.

II. DEFINITIONS

Allergenic products

Allergenic products are biological products which are administered to man for the diagnosis, prevention, or treatment of allergies [21 CFR 680.1(a)] and include Allergenic Extracts and Allergen Patch Tests.

Source material

Allergenic products are usually obtained by the extraction or formulation of active constituents from source material. Source material includes pollen, insects (including venoms), mold, food, chemicals, and animals. It may contain either a single allergen or mixture of allergens.

[1] This guidance document represents the Agency's current thinking on the content and format of the Chemistry, Manufacturing and Controls and Establishment Description sections of a license application for an allergenic extract or allergen patch test. 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.

Biological drug substance

For Allergenic Extracts, the biological drug substance is the sterile intermediate solution produced from the extraction and sterile filtration of source material and contains the biologically active ingredient(s). This intermediate solution is defined as the bulk or stock concentrate. A bulk product is an intermediate solution derived from a single allergenic source and may be filled directly into final containers or used as stock concentrate. A stock concentrate is used in the manufacture of more than one lot of product and is an intermediate solution from which dilutions or mixtures are made [21 CFR 680.3(b)(1)]. For the Allergen Patch Test, the biological drug substance is defined as the allergen (or allergen mix) formulated with the vehicle prior to filling or assembling into the final dosage form.

Biological drug product

The biological drug product is the finished dosage form in its final container. For Allergenic Extracts, it may be the single or mixed allergen extract individually filled, mixed with other allergens, diluted, adsorbed to alum, or lyophilized in the final container. For lyophilized Allergenic Extracts, the diluent used for reconstitution is considered to be a component of the biological drug product. For Allergen Patch Tests, the biological drug product can be an allergen or allergen mix dissolved or suspended in a vehicle, packaged in a final container to be applied to the skin through the use of a suitable holding device (e.g., Finn chamber along with surgical tape), or the biological drug product can be an allergen or allergen mix uniformly dispersed in a gel and coated onto a support (e.g., a plastic sheet cut into patches which are assembled onto surgical tape and directly applied to the skin).

PART 1 – CHEMISTRY, MANUFACTURING AND CONTROLS SECTION

I. DRUG SUBSTANCE

Please refer to the "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances" for further guidance (reference 1 in Appendix A). For regulatory guidance on source materials, please refer to reference 11 in Appendix A**.**

The information that follows may be referenced to a Drug Master File.

A. Description and Characterization

This section should be completed for each biological drug substance identified as being present in the final drug product. This section should contain a description of the active biological substance; this may, if applicable, include the allergen and gel matrix for the Allergen Patch Test. For chemical substances, the description should also include chemical structure; molecular weight; molecular formula; established USP or USAN name; commonly accepted chemical name; physical characteristics, including particle size; and active allergenic component (if known).

B. Manufacturer

1. Identification

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

2. Floor Diagram(s)

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

3. Manufacture of Other Products

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

4. Contamination Precautions

For all areas in which manufacturing or processing is being performed, the following information concerning precautions taken to prevent contamination or cross-contamination should be provided:

- Air quality classification of the room(s) or area(s) in which the 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, cleaning of containers used for storage, 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 identify contamination or cross-contamination. The manipulation of more than one organism in a single area, or the use of any piece of equipment for more than one organism, should be indicated and measures taken to ensure prevention of cross-contamination should be discussed.

For further guidance in this section, see references 2, 3, 4, and 5 in Appendix A.

C. Method(s) of Manufacture

This section should be completed for each drug substance described in I.A. A detailed description of the manufacturing and controls should be provided which demonstrate proper quality control and prevention of contamination. The inclusion of a list of relevant standard operating procedures (SOP) is recommended.

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.

1. Source Material, Raw Materials, and Other Reagents (including components and reagents used in the propagation or processing of raw material)

   The source material contains the active substance (allergen or allergen mix). The active substance(s) is(are) responsible for the biologic allergenic response, either directly or indirectly.

   A summary of the history of the processing of the source material should be submitted. This summary should outline each step involved in processing (including the method of propagation, collection, harvesting, and processing) the source material.

A list of all components used in the propagation and processing of the source material and drug substance and their tests and specifications or reference to official compendia should be provided. This includes the components used in the formulation of growth media for mites and insects, the Allergen Patch Test vehicle, and preservatives and stabilizers. Each lot of raw or processed source material should be accompanied by a certificate of conformance to compendial specifications, where applicable, and/or a certificate of analysis, where provided. For purchased materials, representative certificates of analysis from the component supplier(s) and manufacturer's own acceptance testing results should be provided. Process gases (e.g., air, carbon dioxide) and water are considered raw materials. Validation methods and data documenting the removal of growing media and residues of harmful chemicals from the source material should also be included or in lieu of validation, a description of the tests performed on each lot of source material.

Each lot of source material should be assayed for identity, purity, and potency using validated in-house analytical procedures, **if applicable**. Analytical procedures may include, but not be limited to, RAST, ELISA, IEF, RID, SDS-PAGE, immunoblotting, microscopy, spectroscopy, chromatography, titrimetry, reagent colorimetry. This information should be provided along with specifications and acceptable limits. All test methods should be fully described. The application should include representative data along with chromatograms, spectra, etc. Validation data should include results of studies establishing parameters for linearity, intra-assay precision (repeatability), inter-assay precision (intermediate precision), and recovery. For further guidance in this section, see references 14, 15, 16 and 17 in Appendix A.

In addition to this information:

a. Source Materials Derived from Biological Materials:

   i. Identification (General)

      The genus and species, common name, and microscopic and macroscopic characteristics should be included.

   ii. Epidermal Source Material

      Documentation that the material is obtained from animals in good health prior to the collection of the source material should be included. For animals of the equine genus intended for use as a source material, 21 CFR 680.1(b)(3)(ii) and (iii) requires that documentation be submitted which demonstrates the animal’s immunity to tetanus.

   iii. Mold Source Materials

A description of the propagation, harvest, and downstream processing should be provided. This description should be sufficient to insure the purity, identity through microscopic examination of mold source material. Under 21 CFR 680.1(b)(2), Standard Operating Procedures which describe the performance of these activities and which specify the acceptable limits and kinds of contamination are required to be submitted for review. The Standard Operating Procedures should address, but not be limited to, the following:

- inoculation and propagation
  - -- each step in propagation, from the source, identity (i.e., ATCC catalog number, if applicable) and inoculation of the seed culture to harvest; media used at each step (including water quality), with details of the media preparation and sterilization;
  - -- inoculation and growth of initial and subcultures, including volumes, time, and temperature of incubation; method of transfer of the subculture;
  - -- precautions taken to control contamination;
  - -- in-process testing to insure purity, identity;
  - -- detailed description of the maintenance of the stock culture system, including storage temperatures, frequency and limits of stock culture transfers and/or subcultures, and identification and purity determination procedures; and
  - -- any antibiotics in the medium.

- harvest
  - -- each step in the harvesting procedure, including separation of the source material from the propagation system (precipitation, centrifugation, filtration, etc.), chemicals, and equipment;
  - -- process parameters monitored;
  - -- precautions taken to prevent cross-contamination and introduction of any contaminants;
  - -- criteria for harvest; determination of yields; criteria for pooling more than 1 harvest, if applicable; and
  - -- bioburden monitoring prior and subsequent to harvest.

If the harvested source material is held prior to further processing, a description of the storage conditions and time limits should be provided.

- downstream processing
  - -- cleaning, drying, milling, and grinding of the mold mat;
  - -- inactivation of mold and viability testing; -- method(s) and agent(s) used to make the mold nonviable;
  - -- stage of production where killing is performed;

-- parameters which are monitored;
-- limits and acceptance criteria; and
-- effectiveness.

- purification
  -- methods used;
  -- process parameters monitored;
  -- determination of yields;
  -- criteria for pooling more than 1 batch (if applicable); and
  -- precautions taken to prevent contamination and to monitor bioburden introduced during purification, including the bioburden testing procedure which describes the type and level of contamination, acceptance criteria and limits;
  -- analytical tests (if applicable);
  -- methods used to demonstrate identity, purity, if available, of the source material; and
  -- methods used to measure levels of residual solvents, chemicals, or reagents that may persist from prior processing or purification steps.

The final acceptance criteria for the mold source material should be provided. If the source material is held prior to further manufacture, a description of the storage conditions, including temperature and time limits, should be included.

A typical growth description should be included for a representative species subject to these Standard Operating Procedures.

A list of in-process controls and testing for purity, identity, and viability, as well as time points at which testing is performed, should be included in the flow chart (section I.C.2.) and the Batch Production Record (section I.C.4.). The flow chart should also include a description of the major equipment utilized in the production of mold cultures (i.e., growth flasks, blenders, mills, screens). A brief description and floor diagram of the facility areas, including air quality classification, where inoculation, propagation, and harvesting occur should be submitted in section I.B.2. Precautions taken to control contamination, e.g., during sample removal and transfers, should be provided in section I.B.4.

iv. Food Source Material

Canned and processed foods should not be used as source materials for food extracts. The commercial container/package label from the store where the food is purchased should be part of the batch production record. If the produce is not labeled, the location and identity of the store where purchased should be included in the batch record.

b. Synthetic Chemical Substances that may Represent Complex Mixtures (e.g., synthetic polymers)

Detailed information regarding the source, processing and specifications of these substances should be provided. Identity testing should demonstrate acceptable consistency between batches of source materials.

If any of the above information is included in a Master File, the Master File number and permission to cross-reference the Master File should be provided.

2. Flow Charts

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

3. Drug Substance Processing

a. Allergenic Extracts

The following information should be included:

i. Extraction

Each step of the extraction process should be described including, but not limited to, starting materials, ratio of source material to buffer, temperature and time limits, storage conditions (if stored prior to clarification).

ii. Clarification

Each step of the clarification procedure should be described including, but not limited to, temperature and time limits, filter apparatus and pore size, storage conditions (if stored).

iii. Sterile Filtration

A detailed description of the sterile filtration process, to include the temperature and time limits, filter apparatus and pore size, should be included in this section.

iv. Source Material

Each lot of source material should be assayed for identity, purity, and potency using validated in-house analytical procedures, **if applicable**. Analytical procedures may include, but not be limited to, RAST, ELISA, IEF, RID, SDS-PAGE, immunoblotting, microscopy, spectroscopy, chromatography, titrimetry, reagent colorimetry. This information should be provided along with specifications and acceptable limits. All test methods should be fully described. The application should include representative data along with chromatograms, spectra, etc. Validation data should include results of studies establishing parameters for linearity, intra-assay precision (repeatability), inter-assay precision (intermediate precision), and recovery. For further guidance in this section, see references 14, 15, 16 and 17 in Appendix A.

v. Filling and Labeling

A detailed description of the filling of the sterile drug substance into storage containers, to include temperature, time limits, equipment used, and storage conditions, and the labeling of these storage containers, both

procedure and content, should be included in this section.

b. Allergen Patch Tests

A detailed description should be provided which describes the processing used to produce the drug substance, including micronization and pulverization processes, blending, temperature controls, and aging.

4. Batch Production Record

A completed (executed) Batch Production Record should be submitted which includes the processing of the source material and further manufacture into the drug substance.

D. Process Controls

1. In-process Controls

For all in-process testing indicated in the flow chart, a brief description of sampling procedures and test methods designed to insure the identity, purity and potency of the source material and drug substance should be provided. For testing performed at significant phases of production, the criteria for accepting or rejecting an in-process batch should be specified. For further guidance in this section, see references 3, 15, 16, and 17 in Appendix A.

2. Process Validation

A summary including protocol and results should be provided for the validation studies of each critical process or factor that affects source material or drug substance specifications, i.e., removal of processing chemicals, filter integrity testing, aseptic assembly operations. The validation study reports should document the variability in each process as it relates to final specifications and quality with statistical rigor. For further guidance in this section, see references 2, 3, and 4 in Appendix A.

3. Microbiology

A description and documentation of the validation studies for any processes used for media sterilization, 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" (see reference 2 in Appendix A).

4. Drug Substance Integrity

   Validation testing results which demonstrate that the drug substance remains free of extraneous contaminants during its storage period prior to final filling should be submitted. Acceptable limits for bioburden, storage time and temperature should be provided.

E. Reference Standard (if applicable)

1. Primary Reference Standard

   If a CBER Reference Standard is used, the name and the lot number of the reference standard should be provided.

2. Working Reference Standard

   If an in-house working reference standard is used, a description of the preparation, specifications, testing, and results should be provided. The data from the calibration of the in-house working reference standard against a primary reference standard should also be provided. For further guidance in this section, see references 15, 16, and 17 in Appendix A.

F. Specifications and Analytical Methods

1. Specifications and Tests

   Specifications, acceptable limits, and analytical methods used to insure the safety, identity, purity, potency, as well as lot-to-lot consistency should be provided. Validation of the analytical systems, including validation data, should be provided if this application is a request for the use of a new testing method or equivalent methods and processes. Materials to be submitted include (but are not limited to) chromatograms, instrumental recordings, calibration curves, linear regressions, etc. For testing that does not entail a specific analytical method, such as microscopic determination of purity and identity, specifications and acceptable limits should be provided. Certificates of analysis and analytical results for representative lots should also be included. For further guidance in this section, see references 14, 15, 16, and 17 in Appendix A.

2. Impurities Profile

   A discussion of impurity profiles, with supporting analytical data, should be provided in this section for a drug substance derived from chemicals. Profiles of variants of the drug substance or products produced by interaction of mixed components, as well as non-product related impurities should be included.

G. Reprocessing

A description should be provided of the conditions and criteria which indicate the need for reprocessing the drug substance. Evidence derived from validation studies which demonstrates that the product's identity, purity and potency has not changed during reprocessing should be submitted. For further guidance in this section, see references 4, 15, 16, and 17 in Appendix A.

H. Container/Closure System

A description of the container and closure system and its compatibility with the drug substance should be included. Detailed information concerning the supplier and the results of compatibility, toxicity, and integrity testing should be provided for the container/closure system.

I. Drug Substance Stability (Allergen Patch Tests)

A description of the storage conditions, study protocols and results supporting the stability of the drug substance should be submitted. Data from tests to monitor the biological activity and degradation products, such as oxidized forms, should be included, as appropriate. Data supporting any proposed storage of intermediate(s) should also be provided. For further guidance in this section, see references 7, 12, 13, 16, and 17 in Appendix A.

II. DRUG PRODUCT

This section should contain information on the final biological drug product including all active ingredients and excipients in the final product. If any proprietary preparations or mixtures are used as components, the information should include a complete statement of composition and other information that will properly describe and identify these materials. For all ingredients of human or animal origin, testing results or certificates of analysis demonstrating their freedom from adventitious agents should be provided. Appropriate information may be cross referenced to those under the section on the drug substance. For further guidance in this section, see reference 8 in Appendix A.

A. Composition and Characterization

A list of all components found in the drug product, including the active and other ingredients, with their strengths and batch quantities should be specified (the resultant strengths of the drug product should also be included). For some inactive ingredients, the quantity may be expressed as a percentage or concentration.

1. Drug Substance

   A list of each drug substance should be provided.

2. Excipient

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

   - diluents;
   - bulking agents;
   - adsorbents (other than adjuvants); and
   - stabilizers.

3. Desiccants

   Any agent used to promote dryness should be included in this section.

4. Adjuvant

   This section should contain a list of the chemical formula and precise quantity of each adjuvant. The method for quantity determination should also be specified.

5. Preservative

   Each preservative should be identified by chemical as well as any trade name. The results of the preservative effectiveness validation should be included in the Microbiology section of this document. Reference may be made to other files or compendial sources.

6. Ancillary Components

   For the Allergen Patch Test, a description of the ancillary components used to apply the drug product, such as syringes, or to hold the product in place, such as the support and surgical tape, should be provided.

B. Manufacturer

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

C. Manufacturing Methods

This section should contain a detailed description of the manufacturing process flow of the finished drug product including the sterilization operations, aseptic procedures, lyophilization, and packaging. A flow chart of the process should accompany the description and a listing of all in-process controls and tests performed on the product at each step. A Batch Production Record should be provided which includes complete manufacturing instructions for formulation, including adsorption to an adjuvant and dilution; filling; labeling, including labeling used in-house; and packaging, including cutting of the individual allergen/gel/support patches and their incorporation onto suitable adhesive backing for the patch test panel (see Item D. of this section). References may be made to other sections of this application for more detailed information. For further guidance in this section, see references 3, 5, 15, 16, and 17 in Appendix A.

D. Batch Production Records

One completed (executed) Batch Production Record should be submitted which includes the manufacture, filling, packaging, and labeling of the drug product (see Item C. of this section).

E. Process Controls

1. Process Validation

A summary including protocol and test results should be provided for the validation studies of each critical process or factor that affects the drug product. For further guidance in this section, see references 2, 3, and 4 in Appendix A.

2. Microbiology

a. Allergenic Extracts

A description of the validation studies for any aseptic or microbiologically controlled processes used, such as aseptic filling, sterilization of growth media,

etc., should be submitted in this section. 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" (see reference 2 in Appendix A).

b. Allergen Patch Tests

Allergen Patch Tests are not certified as sterile and are for topical use only. Limits for the number of organisms per dose or volume should be established and the absence of specific pathogenic organisms should be specified. The United States Pharmacopoeia, General Chapter 61, Microbial Limits Tests, should be consulted for guidance.

F. Reference Standard (if applicable)

Please refer to section I.E. for guidance in this section.

G. Specifications and Tests

Specifications, acceptable limits, and analytical methods used for release testing of the drug product, including diluent (if applicable), should be provided. Please refer to section I.F. for detailed guidance. In addition, a description of the selection and storage of retention samples should be provided including the conditions and length of storage. For further guidance, see references 15, 16, and 17 in Appendix A.

H. Reprocessing

Please refer to section I.G. for detailed guidance on this section for the reprocessing of the drug product.

I. Container/Closure System

A description of the container/closure system, including vial sizes, and its compatibility with the drug product to include the supplier(s) and the results of compatibility, toxicity and integrity testing should be submitted.

Even though Allergen Patch Tests are not required to be sterile, evidence of container/closure integrity should be provided.

J. Drug Product Stability

This section should state the proposed expiration dating period for the drug product and the recommended storage conditions. The criteria for determining the date of manufacture, from which the expiration dating period begins, should be defined. For

lyophilized products, a proposed expiration dating period prior and subsequent to reconstitution should be provided.

1. Stability Protocol

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

   - Storage conditions
     -- temperature;
     -- vial sizes; and
     -- vial positions.

   - Assays
     -- potency;
     -- sterility (or microbial limits) or appropriate integrity test;
     -- residual moisture (if lyophilized);
     -- total protein;
     -- preservatives and stabilizers; and
     -- identity.

   - Frequency of testing

   - Detailed statistical plan for interpretation of testing results.

2. Stability Data

   The summary results which support the proposed expiration dating period, under the recommended conditions, in the final container and closure system, should be provided.

   For further guidance in this section, see references 7, 9, 12, 13, 15, 16, and 17 in Appendix A.

III. INVESTIGATIONAL FORMULATION

This section should contain a summary of all differences in formulation, manufacturing processes, or sites between the clinical trials materials and commercial production batches of the drug substance and the drug product. If an investigational biological formulation is different from that of the to-be-marketed finished product, data to support comparability of the two formulations should be provided. For further guidance in this section, see reference 6 in Appendix A.

IV. ENVIRONMENTAL ASSESSMENT

An environmental assessment report should be prepared as outlined in 21 CFR Part 25 with a description of the action that is being considered and should address all the components involved in the manufacture and disposal of the product, including the ultimate use of the product. A statement of categorical exclusion may be provided, if applicable.

V. METHODS VALIDATION

This section should contain information as described in the "Guideline for Submitting Samples and Analytical Data for Methods Validation" (reference 10 in Appendix A).

PART 2 – ESTABLISHMENT DESCRIPTION SECTION

I. INTRODUCTION

In the Federal Register of July 8, 1997, the Food and Drug Administration announced the availability of Revised Form FDA 356h "Application to Market a New Drug, Biologic, or an Antibiotic for Human Use." This section provides guidance on the content and format of information submitted in Section 15, the Establishment Description section, of a License Application for an allergenic extract or allergen patch test.

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;
      - 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 process (or protocol);
- certification that IQ and OQ have been completed;
- a validation data summary;
- an explanation of all excursions or failures; and
- deviation reports and results of investigations for 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 narrative description of the validation process (or protocol) for each of these systems, which includes:

- 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 Documents

1. Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances (1987).

2. Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (1994).

3. Guideline on Sterile Drugs Produced by Aseptic Processing (1987).

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

5. Guideline for Submitting Documentation for the Manufacture and Controls for Drug Products (1987).

6. FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products (1996).

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

8. Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Products (1987).

9. Draft Guidance for Industry on Testing Limits in Stability Protocols for Standardized Grass Pollen Extracts (1997).

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

11. Letter to Source Material Suppliers and Manufacturers of Allergenic Extracts (May 16, 1995).

International Conference on Harmonization (ICH) Guidelines

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

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

14. Validation of Analytical Procedures: Methodology (5/19/97); and Text on Validation of Analytical Procedures (3/1/95).

Laboratory Manuals

15. Methods of the Allergenic Products Testing Lab (1993).

16. Methods of Analysis, Laboratory of Analytical Chemistry, Division of Product Quality Control/CBER (1993).

17. Laboratory of Analytical Chemistry Standard Operating Procedures (1996).