

PREFACE

This document, "Draft Guide to Preparing FDA Form 3210: Application for Establishment License for Manufacture of Biological Products (1995)," is being made available to the public so that the public can review and comment on its usefulness when filling out the recently revised FDA Form 3210 (60 FR 10592). Therefore, this draft document is intended solely for review and comment at this time.

It is the intention of CBER to revise the document based on comments received and publish a final "Guide to Preparing FDA Form 3210." The public is invited to comment on the guide at any time, whether in the draft or final stage and comments received will be used in determining whether further revisions of the guide are necessary.

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INTRODUCTION

This document is intended to provide information for the use of the revised Form FDA 3210, "Application for Establishment License For Manufacture of Biological Products" (ELA) (5/94). This form was recently revised to reflect the information currently being requested regarding facilities used to manufacture biological products intended for license per Title 21, Code of Federal Regulations (CFR) Part 601. The goal of this guide to the Form FDA 3210 is to provide clear written instructions on what information is expected to be contained in an ELA or subsequent supplement. The revised Form FDA 3210 is divided into sections which are intended to logically follow all steps in the manufacturing processes as well as organizational, facility, equipment and related current good manufacturing practices (cGMP) issues. The guide is organized to follow the Form 3210, as it describes the type of information and level of detail expected in response to each question. This document is not intended to describe practices or conditions found to be acceptable by Center for Biologics Evaluation and Research (CBER). That information will be provided in future guidance documents.

Please note, the use of this form in its entirety is intended for the submission of a complete establishment license application (ELA) for a previously unlicensed facility(ies) and company. Use of sections of this form is appropriate when submitting a supplement to an approved ELA. When submitting a supplement to the ELA, only those sections that are relevant to the proposed change need be completed and the form should be signed by appropriate personnel. The Division of Establishment Licensing, CBER, should be contacted in advance of the submission of the supplement with any questions regarding the appropriate use of the form or sections of the form.

If relevant information for the submission of a supplement is already on file with CBER as a part of an approved license application, reference may be made to this information as necessary and appropriate. Specific references should be made to the CBER Reference Number, dates, volume and page numbers) where the information is located. It is expected that the information in such references reflects the current, approved procedures and is also in compliance with current standards and current cGMPs. In any case, specific information should be provided as to how the change described in the supplement (e.g., new product, new or revised process, system or procedure) potentially affects any and all areas in the approved facility(ies).

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Rockville, Maryland 20852-1448

Form FDA 3210 - Application for Establishment License for Manufacture of Biological Products

I. GENERAL INFORMATION

Section I of the Form FDA 3210 (ELA form) requests general information on the entities engaged in the manufacture of the product intended to be licensed.

Question I.A. Name and address of manufacturer for which U.S. license application is being made. Include a copy of the Certificate of Incorporation.

Provide the name, address and phone number of the legal entity applying for the establishment license. This will be the address to which all the CBER correspondence will be addressed. A legal entity may only apply for an establishment license if it is engaged in the manufacture of a product intended to be licensed.

If manufacturing takes place at another location of the company, provide the corporate headquarters name and address for IA., and provide the names) and addresses) of manufacturing locations) in LB. Indicate in IA. or LB. which name will appear on the labeling of the product.

Question I.B. Name, address and registration number of each location of the establishment where actual manufacturing, including testing, labeling and storage, takes place. Identify the manufacturing performed at each location. If this is a shared or contract manufacturing arrangement, describe the functions performed at all locations.

Provide the name, address and registration number of each location of the establishment where actual manufacture takes place, including shared, divided, and contract manufacturing, testing and storage sites for the product. Specify which steps in manufacturing occur at each location (e.g., contract animal test facilities, filling facilities or storage facilities). List the manufacturing location of a company that has correspondence addressed to the corporate headquarters in question LA., along with an indication of which address will appear on the product labeling. The manufacturers) applying for establishment and product licenses is (are) responsible for all pertinent information regarding operations performed at contract locations and such information should be included in the relevant sections) of the form.

Question I.C. Name, address and phone number of responsible individual to whom all official correspondence should be directed and who is authorized to discuss this application.

Provide the name, address and phone number of the Responsible Head (RH) to whom all official correspondence should be directed. The duties of the RH are described in Title 21, CFR Section 600.10(a). This individual should have the ability to exercise control of the establishment in all matters relating to manufacturing and compliance with the regulations and should represent the manufacturer in all dealings with CBER. All correspondence from the manufacturer should bear this individual's signature, or that of an approved alternate or designee. All correspondence from CBER will be addressed to the RH and the staff of CBER will generally not discuss matters related to a pending license application with any other individual unless the designated RH authorizes CBER staff in writing to do so (see Question I.D).

In the event that a contract manufacturer or a location that is remote from the primary manufacturing location is employed, the license applicant may designate an individual at this location as the "Responsible Person" who is authorized to discuss licensing issues with CBER. Primary contact, including all written correspondence, will continue to be conducted through the RH.

Question I.D. Name and address of other responsible official or agent to whom copies of correspondence should be directed.

If desired, the firm may designate an authorized representative to whom CBER will send COPIES of all official correspondence from CBER to the manufacturer. This is often useful for foreign manufacturers who wish to have a representative in the U.S. to facilitate better communication with CBER on licensing matters. This person is referred to by CBER as the U. S. Agent. The number of individuals authorized to represent the RH should be limited so that miscommunication does not arise from numerous individuals discussing pertinent issues. This person will not be authorized to sign official correspondence to CBER from the RH unless he or she has been designated in writing as an alternate to sign correspondence in the absence of the RH.

Question I.E. Name of individual(s) delegated responsibility for release protocol sign-off by the Responsible Head (if it is not the Responsible Head).

For each lot of product manufactured by a licensed facility, lot release protocols are usually submitted to CBER. An individual, other than the RH, may be authorized and designated by the manufacturer to sign the official lot release protocols submitted to CBER. This person is often a member of the Quality Control or regulatory staff of the company.

Question I.F. A brief description of the product or products covered by this application. Include manufacturing flow diagram indicating locations within the facility(ies) where each manufacturing step is performed.

Provide a brief description of the product or products covered by the ELA in the form of a manufacturing flow diagram, including the proper product name, trade name, USAN designation, etc. Ordinarily, a separate ELA form is submitted to CBER which describes the areas of manufacture for each product intended to be licensed. There may be common areas of the facility used for more than one licensed product, such as the warehouse and quality control laboratories. Description of these areas may be made by cross-referencing other submissions (see Introduction).

If the manufacturer has an approved ELA, it may be cross-referenced for a limited amount of information, but the response to this section should describe how each product affects each area of the facility. For instance, the flows of materials and components and manufacturing equipment may differ for each product even though the same areas are used. Dates of submission, volume numbers, page numbers and corresponding CBER Reference Numbers for the cross-referenced information should be provided in response to this question.

Question I.G. General overview of all manufacturing locations.

Provide a general overview of each location, a site plan, a description of all products manufactured at each site, other industry in the immediate vicinity, the distance from farm animals, the square footage of the site and the pest control program. This description should include enough information to determine what other operations are in or near the establishment which might have an effect on the product intended for licensure. List all other products which share manufacture, testing or storage areas with the product intended for licensure. This list should include licensed and unlicensed biological products, medical devices and pharmaceutical products, whether they are intended for research or marketing. Specify the location within the facility where each product is made. Also provide information on other uses of the manufacturing

building, such as offices, locker rooms, etc., as they relate spatially, and functionally, if appropriate, to manufacturing areas.

Question I.H. Provide flow diagrams for the movement of raw materials, product (including in-process product), personnel, equipment and waste within the facility and between locations (if possible).

Provide legible flow diagrams overlaid onto the facility floor plan which illustrate the movement of the raw materials, product at various stages of manufacture, components (e.g., containers, closures, etc.), personnel, equipment and waste. If applicable, describe how product and/or components are moved between locations or buildings. Diagrams should display the flows that are process-related and should not merely indicate the movement into and out of doorways. Illustrate the locations of major pieces of equipment such as autoclaves, fermentors and laminar flow hoods on floor plan(s). Flow diagrams should be accompanied by narrative descriptions.

II. WATER SYSTEMS

Question II.A. What types of water systems are present in the facility? Include information on the quality of incoming source water, connection to the sewer and backflow prevention features.

Provide an overview of all water systems in the facility which will be described more fully in answers to the next questions. Include a list of all water systems present in the facility, location of buildings) where they are housed, and quality of water (i.e., by USP or other standards) that is expected to be generated from each system.

Question II.B. What types of water are used in product manufacture and support areas of the facility?

Identify the quality of water [e.g., potable, USP Purified, Water for Injection (WFI)] used for each stage of product manufacture and production support, including, but not limited to, equipment cleaning, media preparation, clean steam generation, glassware and container/closure washing and rinsing.

Question II.C. Describe the pretreatment system(s).

Provide a narrative description of all pretreatment systems such as sand filters, carbon beds and/or deionization beds, with a rationale for the use of each system. Include descriptions of the materials of construction, filters, instrumentation, computer controls, procedures and reagents used for column regeneration, routine maintenance, etc. Provide a general, legible system diagram with legend, identifying primary system elements.

Question II.D. Describe the systems) used to produce purified water.

Provide a narrative description of all components of the purified water systems) such as deionization beds, reverse osmosis units, ultrafiltration units, vent filter systems and heat exchangers. Include information on the materials of construction, pipe slopes, filters, instrumentation, computer controls, routine maintenance procedures, etc. If purified water is used as a component in product manufacturing (e.g., fermentor media), submit 4

an engineering schematic with legend, showing the system elements described above. If purified water is not used as a component in product manufacture (e.g., feedwater to WFI system), submit a diagram as described in II.C.

Question II.E. Describe the systems) used to produce WFI (include for II.C, D, and E a schematic drawing of each system instrumentation).

Provide a narrative description of all components of the WFI system, such as distillation and reverse osmosis units. Include descriptions of the materials of construction, welding method(s), pipe slopes, filters, instrumentation, computer controls, passivation methods, drop point locations, water temperatures, routine maintenance procedures, etc. Provide a legible engineering schematic with legend, indicating the system elements described.

Question II.F. Describe the validation of each system including specifications, sampling locations and frequency of monitoring for each system. Include data summaries.

Submit protocols and summary data reports for the qualification and validation of all water systems described in previous sections. Include sampling and test methods and acceptance criteria. Data should be reported in tabular format, not simply as "pass/fail". Provide a table summarizing the problems, errors or results that do not meet specifications and subsequent corrective actions taken during the validation period.

Question II.G. Describe the routine monitoring program in place for each system. Include specifications, sampling locations, and frequency and submit data summaries for recent monitoring.

Submit a Standard Operating Procedure (SOP) or narrative description with reference to an SOP(s) detailing the routine monitoring and testing performed for each water system described above. Include sampling sites, frequency and method of sampling, types of tests performed, acceptance criteria (including alert and action limits), and corrective actions taken when specifications are exceeded. Data summaries should be submitted in tabular form. The amount of data submitted should be sufficient to provide an indication of the normal trends seen in the monitoring data. Excursions from specifications should be explored.

III. HEATING VENTILATION AND AIR CONDITIONING SYSTEM(S)

Question III.A. Provide an overall description of the heating ventilation and air condition systems) (HVAC) for the manufacturing facility.

For each air-handling unit (AHU), submit the following information:

1. A narrative description, including but not limited to the number and location of each AHU, rooms/areas serviced by each unit, composition of source air supplied, system design features and location of components, system operating parameters and controls (including temperature and humidity), location of air supply and returns, differential air pressures (inches of water), directional air flow patterns, air velocities, room air quality classifications, any special system features (e.g., containment) and the use of computer controls.
2. A legible floor diagrams) with legend, that illustrates all of the above information, as appropriate (i.e., a diagram that indicates the areas serviced by an AHU as well as the intended room air classification).
3. A legible, representative air system schematic of each AHU that illustrates the location of system

components such as fans, compressors, pre-filters, filters, heating and cooling elements, humidifiers, air diffusers, etc.

Question III.B. Describe fire and smoke control features and routine certification and maintenance procedures.

Provide information regarding system controls which would isolate affected areas and prevent the spread of fire or the dispersion of smoke to unaffected areas. Include a description of routine maintenance and calibration procedures which include the acceptance criteria, procedures for testing components of the system, including HEPA filters, frequency of testing and corrective actions to be taken in case of failure.

Question III.C. Describe validation of each HVAC systems(s) including specifications, sampling locations and frequency of monitoring. Include data summaries.

Submit protocols and summary data reports for the qualification and validation of each HVAC system or AHU described above (including all laminar flow hoods and isolation units used in production and testing). Include information on sampling methods, location of sampling devices, frequencies of sampling, test methods, acceptance criteria, data in tabular format, and conclusions. Provide a table summarizing problems, errors or results that do not meet specifications and subsequent corrective actions taken during the validation period.

Routine environmental monitoring procedures for determination of air quality supplied to manufacturing areas should be discussed and data provided in process-specific sections that follow.

IV. RAW MATERIALS AND ANCILLARY FACILITIES

Question IV.A. Describe areas and procedures for receipt of raw materials and components, including sampling, testing, segregation and storage.

Specify the locations and describe the areas where receipt, sampling, testing and storage occur for raw materials and components. Describe equipment used in sampling and testing, such as dust control devices, laminar flow hoods and laboratory equipment, as well as procedures for each of these operations. Procedures for receipt should include the individuals responsible, parameters checked, paperwork involved, assignment of status, storage location, and the inventory tracking system used. Procedures for sampling should include the individuals responsible, location, number of containers sampled and labeling of sampled containers (e.g., date, volume withdrawn), sampling technique (e.g., aseptic technique if necessary), paperwork involved, and transfer of samples to the testing laboratory. Procedures for testing should include the individuals responsible, location, documentation and review of test results, assignment of expiration dates, and retesting to extend the expiration date. Procedures for storage should include the individuals responsible, location, conditions, segregation, labeling accountability and reconciliation of raw materials and components. In areas where hazardous raw materials are stored or tested, describe safety procedures for handling and steps taken in the event of a spill. Information should be provided on the cleaning and maintenance of all areas discussed in this section.

Question IV.B. Describe the responsibility of the quality control/quality assurance unit in relation to raw materials receipt and testing.

Discuss the relationship between the Quality Control and/or Quality Assurance Unit (QC/QA) and the raw materials program. Specifically discuss the role of QC/QA in sampling, testing and assigning an expiration

date, assigning status (e.g., applying quarantine and release labels to the raw materials), identifying raw materials approaching their expiration date, retesting and reassigning an expiration date, reassigning status, and accountability and reconciliation of raw materials and components. Discuss the responsibility assigned to QC/QA, materials control and manufacturing personnel.

Question IV.C. Are any raw materials tested for identity only, and released on a certificate of analysis for other specifications? If so, please list them.

Some manufacturers choose to qualify vendors using a validation program and subsequently release these materials to production based on an identity test and the certificate of analysis received from the vendor. List any such raw materials, the qualified vendors, and the basis for qualifying the vendors. Also, discuss how often materials are requalified and/or periodically tested for parameters other than identity by the license applicant.

Question IV.D. Describe areas used for storage of raw materials including access and restriction of personnel to these areas.

Discuss raw material and component storage locations, and procedures for controlling and limiting personnel access to these areas. Specify the personnel having access to these areas and their responsibilities. Include environmental parameters such as temperature, air quality, and humidity in a description of storage locations.

V. SOURCE MATERIALS

Question V.A. Name and address of each location from which source materials are obtained. Include license number if applicable.

List the names and addresses of all suppliers of source materials. If the materials are received from more than one location, provide the name and address of each location. A source material is a substance which is further manufactured in some manner, and from which the licensed biological product will be extracted or derived. Examples include plasma for fractionation, and allergenic products source materials such as pollens, mites, insects, mold, food and ascites fluid containing monoclonal antibodies and other starting materials. Some manufacturers of source materials are licensed (e.g., source plasma) while others are not licensed. Provide the license number of the source supplier if applicable. {NOTE: not all plasma is licensed for further manufacturing }

Question V.B. Name and address of each location where partially manufactured source material is obtained under shared manufacturing, divided manufacturing, or short supply provisions. Include the license number or master file number if applicable.

This section should be completed when a partially manufactured source material is received under a cooperative manufacturing arrangement. Specify the type of arrangement as shared manufacturing, divided manufacturing or short supply. Provide the license number of the supplier, if appropriate. In addition, include a list of all manufacturers providing materials under a short supply agreement (21 CFR 601.22).

Question V.C. Describe procedures for accepting source materials. Include the Standard Operating Procedure (SOP).

Specify the locations and describe the procedures for receipt, sampling, testing and storage of source materials. Procedures for receipt should include the individuals responsible, parameters checked, paperwork involved, assignment of status and storage location, and tracking system used. Procedures for sampling should include the individuals responsible, location, number of containers sampled and labeling of sampled containers (e.g., date, volume withdrawn), sampling technique (e.g., aseptic technique if necessary), paperwork involved, and transfer of samples to the testing laboratory. Procedures for testing should include the individuals responsible, location, documentation and review of test results, assignment of expiration dates, and retesting to extend the expiration date. Procedures for storage should include the individuals responsible, location conditions, segregation, and labeling accountability. Also describe the procedures for quarantine and release of the source materials. Provide an SOP or a narrative which describes the process for accepting or rejecting source materials.

Question V.D. Describe areas and procedures for receipt of source materials, including sampling, testing, segregation, personnel restrictions and storage.

Describe the physical locations where the source materials are received, stored and sampled and specify environmental parameters, such as temperature, air quality and humidity. Describe equipment used in sampling and testing, such as dust control devices, laminar flow hoods and laboratory equipment. Specify procedures for preventing contamination during sampling and the environmental controls and monitoring employed during sampling and storage. Discuss the cleaning and maintenance of these areas. Describe procedures that are in place to restrict access by personnel and to assure that unacceptable materials are not placed into production.

VI. PROPAGATION OF HOST SYSTEMS

A. Host Systems

Question VI.A.1. Indicate where the growth, preparation and storage of the master cell bank or seed and manufacturer's working cell bank or seed take place, including materials of construction. (Include areas where validation was performed on the host system).

Provide an overview of the areas where Master Cell Bank (MCB) or seed and Manufacturer's Working Cell Bank (MWCB) or seed were prepared and validated. Specify the locations where these activities occur and provide a general description of the materials of construction, level of environmental control as well as the major pieces of equipment which were used. Include information on storage of MCB and MWCB in response to Question VI.A.3.

Question VI.A.2. Describe procedures in place to prevent contamination and cross-contamination of the host system.

Describe the procedures used to prevent contamination of the host system during propagation to prepare the cell bank or seed. Include a description of the level of cleanliness of the area, segregation of cells during processing, changeover procedures employed when using the area for 8

more than one cell line or strain, gowning of the operators, use of dedicated personnel, dedicated HVAC, equipment, labeling and other identification procedures, etc.

Question VI.A.3. Describe procedures used to track and account for the master cell bank or seed and the manufacturer's working cell bank or seed. Include a description of the security procedures.

Specify all storage locations (on and off site) for master and working cell banks or seeds and the quantities stored at each location. Also specify storage conditions, including temperature, and discuss routine monitoring of storage conditions. Describe all inventory procedures. Discuss how access to storage areas and storage vessels such as liquid nitrogen freezers for cell banks and seeds is limited and secured. Specify who is authorized to remove cell bank or seed vials from storage areas and the mechanism for requesting this material.

Question VI.A.4. Describe features for segregation of production with sporeforming organisms from the host system.

Provide information on where production work with sporeforming organisms is performed, if any (e.g., does not include work with biological indicators (sporeformers) during sterilization validation). Discuss containment features of the areas) and equipment used for processing sporeforming organisms, as well as segregation of these areas from other areas. Describe procedures designed to prevent egress of spores. Discuss special system features, such as HVAC, pressure differentials, etc. Discuss personnel practices in areas where sporeforming organisms are handled including the personnel flow, gowning procedures and segregation. Address all requirements of 21 CFR 600.11(e).

B. Initial Propagation

Question VI.B.1. Describe areas where the manufacturer's working cell bank (MWCB) or manufacturer's working seed (MWS) is taken from storage into the initial growth vessel. Include a description of the room air supply, room surfaces, materials of construction, room class (including containment), gowning, environmental monitoring, cleaning, product changeover procedures and equipment list (including the initial growth vessel).

This response should provide an overview of the areas where MWCB or MWS are taken from storage to the growth vessels) which starts the production process. The information should provide sufficient detail for the reviewer to determine whether the operation is performed within an aseptic environment. The information provided should include the locations where these activities occur and a general description of the materials of construction, level of environmental control (room classifications) as well as the major pieces of equipment (e.g., laminar flow hoods, etc.) which are used. Environmental monitoring information should include limits for viable organisms and nonviable contaminants as well as the methods, locations and frequencies of monitoring for these contaminants. Include methods for identifying and classifying contaminants. Specify the manufacturing activities occurring during monitoring, including the number of operators present and how this relates to actual production conditions. Submit a representative sample of environmental monitoring data for each manufacturing area surveyed during manufacturing operations. Data should be reported in tabular format, not as "Pass/Fail." The amount of data should be sufficient to provide an indication of the normal trends seen in monitoring data. Excursions from specifications should be explained.

Describe all cleaning procedures including those followed on a daily basis, those performed periodically as well as procedures performed during manufacturing activities or between activities. Provide product changeover and campaigning procedures for areas where multiple products are manufactured. Include validated cleaning and clearing procedures designed to prevent cross contamination as well as personnel practices and gowning requirements observed during and following product changeover. Provide an equipment list that details each item, how it is identified, and other products/processes for which it is used (if any). Validation data for equipment cleaning and changeover should be included in response to Question XIV.C.

Question VI.B.2. Describe the method of transfer and procedures used for initial propagation. Include information on validation of the transfer procedures.

Describe receipt of the MWCB or MWS through inoculation into the initial growth vessel, including all procedures followed. Specify in narrative form the steps taken to perform the inoculation or include the SOP. Describe validation of the transfer procedures. Validation of transfer methods should include procedures used, objectives of the validation plan and supportive data. Indicate whether the procedures are open (product exposed) or closed to the surrounding environment.

C. Scale-up

Question VI.C.1. Describe areas where transfers into the scale-up vessels take place. Include a description of the room air supply, room surfaces, materials of construction, room class (including containment), gowning, environmental monitoring, cleaning, product changeover procedures and equipment list (including the scale-up vessels).

Describe areas where all intermediate transfers take place. Guidance on the information to be included in this section is the same as is provided in Question VI.B 1. above.

Question VI.C.2. Describe the method of transfer and procedures used for scale up. Include information on validation of the transfer procedures.

The response should begin with procedures for evaluation of the MWCB or MWS in the initial growth vessel. Describe the method of transfer into all intermediate scale-up vessels and describe the composition and capacity of such vessels, comparing them with the vessels used on the smaller scale. The response should indicate whether the procedures are open or closed to the surrounding environment. Describe the connections used and their ability to be sterilized. Validation of transfer methods should include procedures used, objectives of the validation plan and supportive data.

Question VI.C.3. Describe in detail any "closed systems" used in the transfer process and validation of the "closed systems".

Describe all components of "closed systems" as well as location of input and output and methods of transfer and sampling, including all preparative steps. Include validation summaries of all transfer and sampling procedures as well as of "closed systems". Validation of transfer methods should include procedures used, objectives of the validation plan and supportive data. Provide information on contamination events, including identity of the contaminant(s), potential source and resolution of the problem.

D. Fermentation and Harvest

Question VI.D.1. Describe the area where transfer into the final fermentation vessel takes place. Include a description of the room air supply, room surfaces, materials of construction, room class (including containment), gowning, environmental monitoring, cleaning, product changeover procedures and equipment list.

Discuss the area where transfer into the final fermentation vessel takes place in sufficient detail for the reviewer to determine if the integrity of the inoculum could be compromised during transfer. Guidance on the information to be included in this section is the same as is provided in Question VI.B 1. Specify procedures for spill containment and clean-up. Refer to Question VI.B 1. for information to be provided in response to this question.

Question VI.D.2. Describe the method of transfer and procedures used for transfer into the final fermentation vessel. Include information on validation of transfer procedures.

Describe procedures for evaluation of the fermentor inoculum through inoculation of the fermentation vessel. Include information on the steps required to accomplish a transfer in sufficient detail to allow the reviewer to determine if the integrity of the inoculum could be compromised during transfer. Describe the connections used and their ability to be sterilized. Validation of transfer methods should include procedures used, objectives of the validation plan and supportive data.

Question VI.D.3. Describe in detail any "closed systems" used in the transfer, and fermentation processes and validation of the "closed systems."

Describe all components of "closed systems" as well as location of input and output and methods of transfer and sampling, including all preparative steps. Include validation summaries for all transfer and sampling procedures as well as of "closed systems". Validation of transfer methods should include procedures used, objectives of the validation plan and supportive data. Include information on contamination events, including identity of the contaminant(s), potential source and resolution of the problem.

Question VI.D.4. Describe how the addition of additives to or the sampling from the fermentation system takes place. (i.e., acids, bases, media, gases, in-process purity checks, etc.)

Define the methods by which additions of components and sampling are accomplished including descriptions and validation of aseptic connections, transfers, and sampling procedures. Discuss preparative steps which are taken prior to and following each addition or sampling such as disinfection procedures, steam-in-place of aseptic connections, etc., as well as validation methods and supportive data. Validation of transfer methods should include procedures used, objectives of the validation plan and supportive data.

Question VI.D.5. Describe the equipment used for fermentation. Include materials of construction of tanks, valves, ports, etc.

Provide a complete description of the fermentation vessel and all related components. Specify validation methods that are designed to demonstrate that fermentation equipment is suitable for product contact and steam sterilization and is resistant to rusting, corrosion, and formation of crevices and pits where contamination can occur. Provide information on passivation of equipment when applicable. Describe components of the fermentation system including tanks, valves, ports, gauges, probes, filters, ancillary piping, etc. Specify calibration or validation of components. Indicate if the equipment is dedicated to a single product or shared between products and discuss validated cleaning procedures for product contact surfaces or refer to Question XIV.C.

Question VI.D.6. Describe harvesting procedures and equipment. How is the product separated from the "host system"?

Provide a complete description of the harvesting equipment and methods used to separate the product from the host system. Begin with transfer of the crude product from the fermentation apparatus to the harvesting equipment including validation of this transfer as well as any aseptic connections which are made. Describe in detail any hard piping systems used. Describe validation methods and objectives which are designed to demonstrate that harvesting equipment is suitable for product contact and steam sterilization, and resistant to rusting, corrosion, and formation of crevices and pits where contamination can occur. Validation of transfer methods should include procedures used, objectives of the validation plan and supportive data. Indicate if the equipment is dedicated to a single product or shared between products and discuss validated cleaning procedures for product contact surfaces or refer Question XIV.C.

Question VI.D.7. For all the above procedures, if there is any intermediate storage, describe the containers and areas of the facility used for storage.

For steps described in VI A-D, describe the composition of all containers used for storage of in process product and the effect of leachates, if any. Describe validation methods, objectives, and data which demonstrate that container surfaces are suitable for product contact for the period during which in-process product may be held in them. Such time periods should be defined based on real time in-process product stability or process validation. Submit validation data demonstrating stability or process validation with the accompanying Product License Application (PLA).

Question VI.D.8. Describe the normal maintenance procedures and schedules.

Describe routine maintenance procedures for all equipment and components used during fermentation and harvesting including frequencies with which these procedures are conducted. Include a description of instrument calibration procedures and frequency.

Question VI.D.9. Describe the flows of clean and dirty materials.

Describe in detail how clean and dirty materials are transported to and from fermentation areas including how they are wrapped, whether movement of clean and dirty materials occurs at different times during the day, and whether items are decontaminated prior to leaving the fermentation area. Specify how contamination of clean materials and mixing up of clean and dirty materials are prevented. Describe containment procedures if appropriate.

VII. INTERMEDIATE PROCESSING

A. Isolation and Purification

Question VII.A. 1. Describe the areas used for isolation and purification. Include a description of the room air supply, room surfaces, materials of construction, room class (including containment), gowning, environmental monitoring, cleaning, product changeover procedures and equipment list.

Provide an overview of the areas used for isolation and purification in sufficient detail for the reviewer to determine whether exposed operations are environmentally protected. Guidance on the information to be included in this section is the same as is provided in Question VI.B 1. above.

Question VII.A.2. Describe the method of transfer and procedures used for this step. Include information on validation of the transfer procedures.

Provide a description of how the product and buffers (if applicable) are transferred throughout the isolation and purification steps. Describe equipment (e.g., piping, tanks) and procedures (e.g., aseptic connections) used in the transfer of these components. Specify whether these operations are considered "open" or "closed" and provide the appropriate validation information. Validation of the transfer methods should include the methods used, objectives of the validation plan, and supportive data.

Question VII.A.3 Describe special chemical purification equipment such as columns, equipment used for precipitation, dialysis and other chemical procedures. Describe the preparation, sanitization/sterilization and storage of this equipment. Include any appropriate validations.

Provide a complete description of the equipment used in chemical purification. Specify the manufacturing step in which the equipment is used, and describe how the equipment is cleaned, identified as such, assembled and stored during periods of non-use and refrigerated if applicable. Indicate whether the equipment is dedicated or shared between different products and discuss validation of cleaning procedures or refer to Question XIV.C. Include methods, objectives of the validation plan, and supportive data for validation procedures submitted for these steps.

Question VII.A.4. Describe special mechanical purification equipment such as filters, ultracentrifuges, homogenizers, etc. Describe the preparation, sanitization/sterilization and storage of this equipment. Include any appropriate validations.

Provide a complete description of the equipment used in any mechanical purification. Specify the manufacturing step in which the equipment is used and discuss how the equipment is cleaned, identified as such, assembled and stored during periods of non-use. Include methods, objectives and summaries of supportive data for validation studies submitted for these steps. Indicate whether the equipment is dedicated or shared between different products and discuss validation of cleaning procedures or refer to Question XIV.C.

B. Inactivation

Question VII.B.I. Describe the areas where inactivation occurs. Include a description of the room air supply, room surfaces, materials of construction, room class (including containment), gowning, environmental monitoring, cleaning, product changeover procedures and equipment list.

Provide an overview of the areas used for inactivation. Guidance on the information to be included in this section is the same as is provided in Question VI.B.1. above. Discuss separation of inactivated and non-inactivated in-process product.

Question VII.B.2. Describe the method of addition of the inactivation agent and/or procedures used for this step. Include information on validation of the transfer procedures.

Provide a description of the methods used to add/transfer the inactivation agent and/or the procedures used which result in inactivation (e.g., steps used to remove viral contaminants). Validation of transfer methods should include procedures used, objectives of the validation plan and supportive data.

Question VII.B.3 Describe the containers and areas used for storage of product during and after inactivation. Include specific information on segregation from non-inactivated product during storage.

Provide a description of the containers and areas used for storage of the product during and after inactivation. Specify materials of composition of the storage containers and the effect of leachates if applicable.

C. Additional Processing

Question VII.C.I. Describe the areas where additional processing such as addition of adjuvants, preservatives, conjugation, pooling of bulk concentrates, etc., occur. Include a description of the room air supply, room surfaces, materials of construction, room class (including containment), gowning, environmental monitoring, cleaning, product changeover procedures and equipment list.

Provide an overview of the areas used for additional processing including the addition of adjuvants, preservatives, conjugation and/or pooling of bulk concentrates or other steps not described in other parts of the form. Guidance on the information to be included in this section is the same as is provided in Question VI.B.1. above.

Question VII.C.2 Describe the methods used to conduct the additional processing.

Describe the methods (e.g., additions, transfers, chemical reactions) used to conduct the additional processing. Describe equipment (e.g., piping, tanks), placement and procedures (e.g., aseptic connections) used in the transfer of these components. Specify whether these operations are considered "open" or "closed". Supply validation information for all transfer methods. Validation of transfer methods should include procedures used, objectives of the validation plan and supportive data.

Question VII.C.3 Describe containers and areas used for storage of in-process product.

Provide a description of the containers and areas used for the storage of in-process product. Describe the materials of composition of the storage containers and the impact of leachates if applicable.

VIII. FORMULATION AND FINAL PRODUCT PREPARATION

A. Final Bulk

Question VIII.A.I. Describe areas, procedures and equipment for formulation of the final bulk. Include a description of the room air supply, room surfaces, materials of construction, room class, gowning, environmental monitoring, cleaning, product changeover and equipment list.

Provide an overview of all areas used for the formulation of the final bulk. Guidance on the information to be included in this section is the same as is provided in Question VI.B.1. above.

Question VM.A.2. Describe containers and areas used for storage of intermediate (presterilized final bulk) product.

Describe the containers and areas used for the storage of the presterilized final bulk. Clearly identify the areas (e.g., cold boxes) and describe the environmental controls (e.g., temperature) in detail. The materials of composition of the storage containers (e.g., composition of glass and plastic) should be described and the impact of leachates should be discussed in this section. Specify storage periods and parameters and submit the supportive real-time stability data to the PLA.

B. Sterilization of the Final Bulk

Question VIII.B.I. Describe areas, procedures and equipment used for sterilization of the final bulk. Include a description of the room air supply, room surfaces, materials of construction, room class, gowning, environmental monitoring, cleaning, product changeover procedures and equipment list.

Provide an overview of the areas used for the sterilization of the final bulk. Guidance on the information to be included in this section is the same as is provided in Question VI.B.1. above.

Question VIII.B.2. Describe the container and areas used for storage of final sterilized bulk product.

Provide a description of the containers and areas used for the storage of the final sterilized bulk. Areas (e.g., cold boxes) should be clearly identified and the environmental controls (e.g., temperature) should be described in detail. The materials of composition of the storage containers (e.g., composition of glass and plastic) should be described and the impact of leachates should be discussed in this section.

C. Filling

Question VIII.C.1. Describe areas, procedures and equipment used for filling of the final containers. Include a description of the room air supply, room surfaces, materials of construction, room class, gowning, environmental monitoring, cleaning, product changeover procedures and equipment list.

Provide an overview of the areas used for the filling of final containers. Guidance on the information to be included in this section is the same as is provided in Question VI.B.1. above.

Question VIII.C.2. Describe media fill validation. Include data summaries.

Submit the SOP describing the media fill validation study. The SOP should include the following information: statement of purpose, individuals involved equipment list, environmental conditions (e.g.,

air quality, temperature, humidity) and monitoring results (e.g., surfaces, air, personnel), operational conditions (e.g., number of employees, length of time, number of vials/ampules), type and qualification of media, preparation of media and filling components (e.g., vials, stoppers, filling heads), cleaning procedures, incubation conditions (e.g., time, temperature, position of the vials), acceptance criteria and investigational procedures and corrective actions to be implemented if criteria are exceeded. Include a description of the frequency and operational parameters (e.g., shifts and number of runs) for the periodic revalidation program. Provide the supportive data for all media fills used to validate aseptic filling. Include in tabular format, the identity of all microorganisms isolated during the validation studies as well as the associated deviation reports including the probable source of contamination. Describe how each of the aforementioned conditions observed during the media fill validation compares to conditions observed during actual production operations, as specified in the Master and Batch Production Records.

D. Lyophilization

Question VIII.D. Describe areas, procedures and equipment for lyophilization of the final containers. Include a description of the room air supply, room surfaces, materials of construction, room class, gowning, environmental monitoring, cleaning, product changeover procedures and equipment list. Validation should be described in the validation section. If filled, partially stoppered containers are transported to a separate area for lyophilization, describe transfer procedures in detail.

Provide an overview of the areas used for the lyophilization of the final product. Guidance on the information to be included in this section is the same as is provided in Question VI.B.1. above. In addition, include a description of the spatial relationship between the lyophilization equipment and the filling lines, method of transferring filled containers to the lyophilizer (e.g., in a laminar flow hood/container) and any intermediate storage or freeze-down. Provide information regarding validation of aseptic processing during product transfer and lyophilization. Qualification of lyophilizer and validation of the lyophilization cycle should be submitted in response to Question XIV.B. Validation of cleaning procedures (e.g., CIP/SIP) should be included in response to Question XIV.C.

E. *In Vitro* Diagnostics

Question VIII.E. Describe areas, procedures and equipment for finishing of *in vitro* diagnostic product that are not covered in other sections of this application. Include a description of the room air supply, temperature and humidity, materials of construction and room surfaces, room class, environmental monitoring and personnel gowning, cleaning procedures, product changeover procedures, and equipment list.

Guidance on the information to be included in this section is the same as is provided in Question VI.B.1. above.

F. Capping

Question VIII.F.1. Describe the areas and equipment used for capping of the final containers, include a description of the room air supply, room surfaces, materials of construction, room class, gowning, environmental monitoring, cleaning, product changeover procedures and equipment list.

Provide an overview of the areas used for the capping of final containers. Guidance on the information to be included in this section is the same as is provided in Question VI.B.1. above. Also describe conditions of transport and storage of stoppered, uncapped vials between areas.

Question VIII.F.2. If unlabeled vials are stored before labeling, describe the areas and procedures used to store the product.

Specify storage areas (e.g., cold boxes) for unlabeled vials as well as environmental controls (e.g., temperature). Provide a list of other products stored in the same location(s). Describe procedures including the type of container in which the vial/ampules are stored, labeling of the container, accessibility to the container (e.g., individuals responsible) and precautions taken to prevent the mix-up of unlabeled, final container material.

G. Packaging and Labeling

Question VIII.G.1. Describe the areas and equipment used for labeling and packaging of final containers. How is physical separation accomplished? What procedures are in place to prevent mix-ups or mislabeling of final product?

Specify the location and describe the areas where labeling and packaging occur for final container material, including environmental parameters (e.g., temperature). Also describe cleaning and maintenance of these areas. Describe the equipment used in labeling and packaging including calibration and maintenance procedures. Describe procedures used to prevent mix-ups or mislabeling of final product. Procedures should include individuals responsible, line clearance parameters and reference to an SOP, labeling control, and a description of documentation, quality control or quality assurance oversight/sampling during these procedures.

Question VIII.G.2. Indicate where labeling is stored and how accessibility to the area is controlled.

Identify the areas used for the storage of all labeling. Describe containers/boxes in which labeling may be stored. Address accessibility by personnel to labeling storage location(s), specifying which personnel have access to these areas, their responsibility and the procedures for controlling access to both secure and non-secure label storage. Discuss documentation relevant to label security.

Question VIII.G.3 Describe the labeling reconciliation procedure.

Provide the SOP for labeling reconciliation. Procedures for reconciliation should include individuals responsible, parameters checked, documentation, label destruction procedures and a course of action if labeling does not reconcile within specifications.

Question VIII.G.4. Describe areas used to store final labeled product. Include information on segregation of released and unreleased product.

Specify storage areas (e.g., cold boxes) for final labeled product as well as the environmental controls (e.g., temperature). Provide a list of other products stored in the same area. Describe remote distribution sites if used to store unreleased product. Specify physical parameters for the segregation of released and unreleased product including method for inventory control (manual or computerized).

IX. COMPUTER SYSTEMS

Question IX.A. Describe all processing steps which are computer controlled. Describe each system used in these steps. Include a schematic diagram of the system and the functional statement.

Identify all manufacturing processes (e.g., product processes, quality control, packaging, labeling, holding and distribution functions) which are monitored or controlled by computer systems. Provide a system schematic which identifies all major system components, interfaces and distribution systems. Describe each computer system used to control manufacturing processes, include a statement of functional requirements, a listing of system components including hardware, software, input and output devices (e.g., thermocouples, pressure and flow rate gauges, alarms, printers and monitors), and equipment under computer control. Define the scope and range of computer controls for each critical manufacturing process (e.g., monitoring and adjusting process parameters and initiating process steps). Describe the physical location and environment of each computer system. Provide documentation that demonstrates appropriate training and qualifications of personnel responsible for monitoring and operating computer controlled systems. Describe records maintained by computer systems and include a description of the use (e.g., integration into batch records) and review of these records by manufacturing and quality control personnel.

Question IX.B. Describe any computer system used to control the tracking and/or status of raw materials, in-process materials, or final product.

Describe each computer system that is used to track and monitor the status of raw materials, in process materials or final product. The description should include the following: statement of functional requirements, system schematic, type of software, hardware, input (e.g., barcode vs. operator) and output devices and distribution systems, type of information recorded, use in manufacturing process (e.g., maintenance of expiration dates and inventory control), and program for maintenance of data integrity including updates and verification.

Question IX.C. Describe the validation and security of the hardware and software of each system.

Provide validation summaries for each computer system including the following: installation qualification (IQ) - purpose, results, conclusions; operational qualification (OQ) - purpose, results, conclusions; performance qualification (PQ); types and number of tests performed; acceptance criteria; summary of test results; system performance during simulated worst-case scenarios and actual production runs; requalification and revalidation criteria and procedures. Describe the security procedures which provide control of access to data entry, data read, and process control for all appropriate systems. Describe override capabilities in the system which permit process intervention. Describe procedures and methods which identify and document users and operators with particular data entry and operational functions. Describe the disaster recovery plan for data retrieval and process restoration in the event of loss of computing capability or loss of electrical supply. Include a description of the maintenance and storage of back-up files.

Question IX.D. Indicate where the software was developed and describe procedures for program updates.

Identify the organization responsible for the development of software used in the manufacturing processes. If software is commercially available (e.g., off-the-shelf), describe the testing methods used to assure that such software satisfies functional requirements. If software is developed by a vendor and/or internally, describe the development procedures, the auditing performed, and the testing methods to assure that such software satisfies functional requirements. For all software, describe the location and storage requirements of the source code, and accessibility to the source code. In addition, describe software change control procedures including implementation of new, updated or revised programs and subsequent testing and evaluation.

X. SUPPORT AREAS

Question X.A. Describe the areas and equipment used for media and buffer preparation. Include a description of the room air supply, room surfaces, materials of construction, room class, gowning, environmental monitoring, cleaning, product changeover procedures and equipment list.

Describe all areas and equipment used for the preparation of media and buffer components used in manufacture. Guidance on the information to be included in this section is the same as is provided in

Question X.B. Reference may be made to detailed diagrams included in response to other sections of this form.

Question X.B. Describe the areas used for cleaning of equipment. Include a description of the room air supply, room surfaces, materials of construction, room class, gowning, environmental monitoring, cleaning, product changeover procedures and equipment list.

Describe all areas and equipment used for the cleaning of equipment used in manufacturing and testing. Refer to Question VI.B.1. for information to be provided in response to this question. Reference may be made to detailed diagrams included in response to other sections of this form.

Question X.C. Describe maintenance and service areas of the facility.

Specify the locations and functions of the maintenance and service areas of the facility. Describe the areas systems and equipment serviced by these units, the impact (if any) of the physical location of these areas on controlled manufacturing areas and the method of access to these areas. Discuss how access to these areas is limited. Include information concerning control units of special systems (e.g., automated, computer controlled environmental monitoring systems) located in these service areas, in section XIV.

Question X.D. Describe the waste handling and disposal systems for the facility. Do decontamination and sterilization take place in the same area? If so, please describe procedures to prevent mix-ups.

Provide a detailed description of the waste handling and disposal systems for both liquid and solid wastes for all areas of manufacture and testing. Include the following information: description of the processing of

solid and liquid wastes with inclusion of specific SOPs; diagrams detailing the flow of the waste exiting the facility; design features and validation information for specialized inactivation or kill tank systems or reference to section XIV; indication of the capacity of such systems; description of control parameters, alarms or indicator signals as well as operating parameters such as temperatures and lengths of inactivation or decontamination. Describe all other equipment used to decontaminate waste (e.g., autoclaves), and provide validation information. Reference responses to Question XIV. If equipment such as an autoclave is used to decontaminate waste and to sterilize equipment and materials, supply the SOPs that describe the segregation of these operations (e.g., time and space) in order to prevent mix-ups and cross contamination.

Question X.E. Describe the areas used for sterilization and depyrogenation of equipment and final container components.

Describe all areas and equipment used for the preparation (e.g., wash, stage, wrap, hold), sterilization and depyrogenation of equipment and final container components with reference to the appropriate diagrams. Similarly, describe post-sterilization and post-depyrogenation holding areas, procedures, and associated state of post-processed goods and articles (e.g., containerization, wrap, expiration dating, status indicator). Refer to Question XIV, as needed, for equipment design and validation. Facility and equipment information should be included as outlined in Question VI.B.1. and should include the following information for all areas and equipment above: air quality and room classification, list of relevant SOPs, procedures for product and process changeover, cycle parameters and descriptions (e.g., stopper or vial wash-siliconization processes).

Question X.F. Describe areas used for storage of in-process materials and final product.

Refer to floor plans and responses in other sections of the form as appropriate. Provide the following information: materials of construction; location of refrigerators, cold rooms and freezers; description of storage parameters such as temperature; control and monitoring of such parameters; a description of the monitoring devices (with reference to section XIV); capacity of areas or units; list of other materials stored in these areas or units to include materials used for other licensed and unlicensed products and their intended use; the status of each material, indicating whether it is under quarantine or has been released by Quality Control; and a detailed description of how materials are labeled and segregated (physically and/or spatially) in these areas to prevent mix-ups.

XI. QUALITY CONTROL AREAS

Question XI.A. Define the quality control unit and how its reporting structure relates to the rest of the organization. What is the relationship between Quality Control (QC) and Quality Assurance (QA)?

Describe the relationship between Quality Control (QC), manufacturing and Quality Assurance (QA) units. Provide information on reporting authorities, documentation, sign-off authority for review of deviations and investigations.

Question XI.B. Describe the facilities where testing is performed. Include a copy of the written agreement with any contract testing site.

Specify all laboratories/areas where QC testing is performed and QC samples are stored (both onsite and contract testing). Provide a general description of the materials of construction and level of environmental control. Specify the storage locations for stability samples. Include a copy of the written agreement

associated with contract testing sites. Provide information on animal facilities for testing in Part XII. Describe Sterility test areas in Part XI.E of this section.

Question XI.C. Describe the separation of functions using microorganisms. Describe the storage of samples and standards. Describe the calibration and maintenance of equipment.

Provide a list of microorganisms maintained in the facility and describe the use of these microorganisms (e.g., Candida albicans; growth promotion quality testing). Specify the areas where QC samples and reference standards are stored. Describe the calibration and maintenance of equipment (e.g., freezers) used to store QC samples and reference standards.

Question XI.D. List major equipment used in QC testing of the product.

List the equipment used in QC testing of the product and specify where it is located and whether the equipment is used for testing other products. Discuss precautions taken to prevent cross-contamination as applicable: Discuss the routine calibration and maintenance of such equipment, including use logs, etc.

Question XI.E For sterility test areas, describe the precautions taken to prevent false positives from occurring.

Describe the sterility test area(s), equipment, cleaning procedures for the area(s), environmental monitoring of the areas) (particularly during dynamic conditions) and personnel gowning. Place emphasis on procedures designed to prevent the occurrence of false positives and on procedures designed to investigate and document whether contaminants are false positives.

XII. ANIMAL FACILITIES FOR TESTING

Question XII.A. What animals are used in the testing of product(s)? Include the types of animals and how they are used for each specific product. Include numbers of animals and the number of animals per cage. Is there a sentinel animal program in place?

Specify animal species and strain for each animal test performed. If there is a sentinel program in place, specify the source of these animals and describe how sentinel animals are tested and maintained.

Question XII.B. Give the address of locations and outline the following features of all animal facilities used in testing:

- 1. HVAC System**
- 2. Water system.**
- 3. Materials of construction.**
- 4. Flow of materials and animals.**
- 5. Relationship to other manufacturing areas.**
- 6. Segregation procedures for multi-product areas.**
- 7. Support areas for cage washing, food handling, etc.**

Provide the address and features listed for all animal testing locations including contract manufacturing locations.

Question XII.B.1 HVAC System

Indicate whether the HVAC system which supplies animal facilities is segregated from air supplies to other areas of buildings where manufacturing operations occur. Indicate whether air supplied to animal areas is HEPA filtered. Specify the number of air changes per hour, temperature and humidity controls, and pressure differentials between adjacent areas and corridors.

Question XII.B.2. Water System

Describe the method used to water animals, e.g., individual water bottles or central water source which directly feeds each of the animal cages. Describe the water system and the quality of water which supplies animal facilities (or reference Question II of this application). Discuss water monitoring procedures and frequencies.

Question XII.B.3. Materials of Construction

Describe the compositions of walls, floors and all surfaces. Highlight the features of the materials of construction that render them impermeable, easily cleanable and resistant to deterioration and destruction.

Question XII.B.4. Flow of Materials and Animals

Describe the flow of animals and other materials such as food and bedding. Describe the flow of all waste and contaminated materials and discuss the conditions under which these materials are transported out of animal facilities. Include procedures for decontamination and inactivation where appropriate. Discuss the segregation of these flows so as to prevent cross contamination.

Question XII.B.5. Relationship to Other Manufacturing Areas

Indicate all other operations and activities which occur in buildings where animal facilities are located. Describe how animal facilities are physically isolated from other areas of buildings which are not dedicated to housing animals. Specify all procedures which are in place to prevent cross contamination between animal areas and manufacturing areas.

Question XII.B.6. Segregation procedures for multi-product areas.

Identify all areas in which multiple products are tested and describe procedures in place to prevent cross-contamination or mix-ups of products and animals. If multiple activities occur simultaneously in the same area, discuss how personnel operations and practices (e.g., gowning) are employed so as to prevent contamination. Discuss identification methods for animal cages and individual animals if applicable.

Question XII.B.7. Support areas for cage washing, food handling, etc.

Describe all support areas and the major equipment which are used in each area. Include procedures for operations which are carried out in support areas such as cage washing, autoclaving of feed and bedding as well as their storage, waste treatment, decontamination and removal.

Question XII.C. Describe animal quarantine procedures.

Describe animal quarantine procedures for each species of animal used for testing, upon receipt, and procedures employed for observation of animals during this period. Specify the qualifications of the individuals who observe the animals during the quarantine period.

Question XII.D. Do the same personnel work in animal and manufacturing areas on the same day? Describe special personnel practices and gowning for the animal facility. Please provide a personnel flow diagram.

Describe procedures followed by personnel to insure that contamination of manufacturing areas does not occur. Include information concerning gowning, changing and showering procedures. Specify circumstances under which animal facility personnel would be prohibited from entering manufacturing areas, and procedures in place to control this access. Include a personnel flow diagram or reference to a diagram submitted in another section.

XIII. ANIMAL FACILITIES FOR PRODUCTION

Questions XIII.A and B.

Guidance on the information to be included in this section is the same as provided in Part XII above, Animal Facilities for Testing, Questions A and B.

Question XIII.C. Animal Source. Are animals bred on-site or are they received from another breeding facility? If received from another facility, describe procedures for receipt of animals.

If animals are bred at another facility, include a discussion of the breeding facility's criteria, procedures for shipment of animals as well as shipment conditions and validation information supporting these procedures. Also describe criteria for acceptance of animals into the production facility. Discuss procedures for disinfecting incoming animal shipping containers. Specify the length of time animals may be held in shipping containers prior to transfer to cages.

Question XII.D. Describe animal quarantine procedures.

The information is the same as provided in Part XII, Animal Facilities for Testing, Question C.

Question XIII.E.1. Animal Health. Describe veterinary care, including routine testing and diagnostic analysis provided by veterinary personnel and frequency of animal site visits.

Specify routine testing and diagnostic analysis conducted on animals both before and during their use in production. Discuss procedures which are followed to determine the cause of unexpected illness or death of animals both before and during their use in production. Indicate whether or not a veterinarian is always present on-site or specify the frequency of site visits if this is not the case.

Question XIII.E.2. Who observes the animals on a daily basis for general health during quarantine and production periods?

Discuss the qualifications of the personnel who observe animals on a daily basis. Specify the criteria used to evaluate animal health and procedures which are followed to notify veterinary personnel in the event of unexpected illness or death of an animal.

Question XIIF.1. Describe cleaning procedures including frequencies for cages, water bottles,

sippers, etc. How often is bedding changed?

Describe, in narrative form or in an SOP, the cleaning procedures, including frequencies of cleaning of equipment and frequency with which animal bedding is changed. Indicate whether bedding is autoclaved before use.

Question XIII.F.2. Describe animal 1 room cleaning procedures. Where are animals housed during cleaning?

Describe in narrative form or in an SOP, animal room cleaning procedures, including frequencies. Describe the conditions under which are housed during animal room cleaning and the approximate time during which animals remain outside of their normal environment.

Question XIII.F.3. What is the method of feed pasteurization? How was this procedure validated?

Discuss the methods for reducing co contamination of feed, the SOP for validation of this process and supportive data. Indicate the acceptable limit for indigenous microbial contamination in the animal feed.

Question XIII.G1. Describe the areas and environmental conditions for priming, inoculation, tapping pooling and processing procedures which take place in animal production areas.

Describe environmental conditions including viable and nonviable contaminant limits and the room classification (or area classification in the case of a laminar flow hood) where these operations are performed. This information should be provided for each step during which the product or components are manipulated. Specify environmental monitoring frequencies as well as procedures for cleaning and product changeover for multi-product facilities. Submit a representative sample of environmental monitoring data for each animal production area surveyed during production. Data should be reported in tabular format, not as "Pass/Fail". The amount of data should be sufficient to provide an indication of the normal trends seen in monitoring data. Excursions from specifications should be explained.

Question XIII.G.2. How are animal cages labeled?

Describe the information which is posted on animal cages such as: product, lot number, inoculation date(s), tapping date(s), to number, etc.

Question XIII.G.3. Describe any containers or equipment used during production.

Provide a complete description of all equipment used for production in the animal facilities. Information on calibration and maintenance as well as validation methods should be provided or reference information provided in section XIV as appropriate. Provide validation methods and supportive data which demonstrate that container surfaces are suitable for product contact for the time period during which in-process product may be held in the container. Time periods should be based on real time in-process product stability or process validation submitted to the PLA.

Question XIII.H.1. Describe the animal technician training program.

Describe the training program for animal technicians in detail including any refresher training which is offered or required. Specify any background qualifications required of animal technicians as well as the qualifications of the personnel responsible for training. Specify whether animal technicians are trained to perform specific tasks or cross-trained to perform all technical tasks in the animal facility.

Question XIII.H.2. Do the same personnel work in animal and other manufacturing areas on the same day?

If personnel are allowed to work in other manufacturing and animal production areas, describe procedures followed by personnel to insure that contamination of manufacturing areas does not occur. Include information concerning gowning, changing and showering procedures. Specify circumstances under which animal production facility personnel would be prohibited from entering other manufacturing areas, and procedures in place to control this access.

Question XIII.H.3. Describe special personnel practices and gowning for the animal facility. Please provide a personnel flow diagram.

In addition to gowning and showering procedures which must be followed by personnel entering animal production areas, discuss any health requirements as well as other requirements which personnel must meet in order to enter animal production areas. For example, specify whether personnel are required not to have had contact with certain animal species for a minimum period of time prior to entering animal production areas. Include a personnel flow diagram or reference to a diagram submitted in another section.

XIV. CALIBRATION AND VALIDATION

Question XIV.A. For all major systems such as waste disposal, Clean-In-Place (CIP), Steam-In-Place (SIP), compressed air, etc., please provide a description of the validation studies performed including the results. Include a table of all validations done and the related protocols and a summary of the results of each major system. Include: 1. Installation Qualification 2. Operation Qualification 3. Performance Qualification 4. Revalidation

For all those major facility systems that are not fully described in response to other sections) of this form, provide detailed calibration, qualification and validation information. Make reference to other sections where appropriate.

Provide detailed summaries of the operations performed during the qualification and validation studies. Include an explanation of the purpose of the study, the operations performed, the significant results of each study and the conclusions drawn. Information and data presented in tabular format will assist in the review, i.e., a tabular listing of all studies performed, their purpose, document number, limits and acceptance and results. If specific recommendations for changes to operations or conditions were made by the vendor, contractor or internal unit performing the operations, these should be noted and explained. Specify the group or unit performing each operation, whether an internal engineering unit or a contractor. Include information on system operating parameters and specifications in tabular format.

Specify the frequency for requalification and calibration of each major system. Provide a master plan or SOP for the routine calibration of all systems with indication of the unit or group responsible for such calibration. Describe conditions that necessitate revalidation, initiation of revalidation, and associated documentation. Provide a tabular listing of relevant SOPs (including SOP numbers) related to validation.

Question XIV.B. For major pieces of equipment, please provide a description of the validation studies performed including the results. Include a table of all validations done and the related protocols and a summary of the results for each piece of equipment.

Provide similar information, data and report summaries as described in section XIV.A. for all major pieces of equipment such as autoclaves, dry heat ovens, lyophilizers, glass washers and hoods. In addition, provide diagrams of the design of individual units and load configurations where appropriate. These diagrams should clearly depict the placement of monitoring device controls and other equipment, such as thermocouples and spore indicators used in the validation of autoclave cycles. Include validated equipment cycle parameters and specifications in tabular format with reference to applicable qualification and validation documents, limits, and results. Information and data presented in tabular format will assist in the review. As requested in Question XIV.A., provide detailed information on the calibration and requalification and/or revalidation of the major pieces of equipment. Include frequency of maintenance, circumstances governing requalifications or revalidations, the group or unit responsible, documentation of operations and a list of relevant SOPs.

Question XIV.C. For critical processes such as cleaning of product contact parts and major equipment in product contact, disinfection, product changeover, etc., please describe the validation studies that were performed and the results of each.

Include detailed summaries of all other qualification and validation studies in this response or in response to the PLA form, whichever is more appropriate, (e.g., validation of the re-use of column purification resins would be more appropriately addressed in the PLA). These summaries should include a description of the purpose of the study, the study conditions and tests or assays performed, the acceptance criteria, the results and conclusions that were drawn. Include specifications that were set as a result of these studies. Describe all change-over and campaigning procedures, including validation of cleaning procedures for shared product contact equipment, and provide the appropriate validation protocols and supportive data. List the relevant SOPs and supportive data presented in tabular format. Discuss appropriate requalification and/or revalidation conditions and intervals.

XV. RECORDS

Question XV.A. Describe the relationship between the master production record and each batch production record.

Describe how the Batch Production Record is created from the Master Production Record, outlining procedures used for verification of accuracy of reproduction. Explain any differences in format or information. Describe the procedures for revising both Batch and Master Records. Provide SOPs and other documentation describing the inclusion of reports of variation/deviation in manufacturing into the batch records. Provide a definition of what constitutes a variation/deviation or actions requiring a change in documentation. Outline the traceability of these records. Provide a copy of the Master Production Record.

Question XV.B. Explain the preparation of records and sign off authority within the organization.

Discuss the preparation, review and sign-off of all production and testing records, including the following: individuals responsible for record preparation, SOPs for review and evaluation of new records and revisions to existing records (e.g., change control procedures), and procedures and individuals responsible for final sign-off and approval of all new records and revisions to existing records. Describe how all materials and components used in manufacture are identified and traced in the lot number and/or batch record (e.g., how raw material part numbers are incorporated into the records). Explain the authority and

oversight of the designated RH and Quality units in this process (or refer to information contained in other sections).

Question XV.C. How are records assembled, stored and accessed?

Explain how the final production and testing records are assembled, detailing all the elements necessary for a complete record and how these elements are accessed and compiled. Discuss how different records interrelate, e.g., inclusion of QC results and data in the batch production record. Specify conditions and locations for storage and retention of all records and describe restricted access to such records. Indicate the form of the records, e.g., originals or true copies, if applicable.

Question XV.D. Who reviews the records for each lot prior to release of the lot? Describe the method of documenting such reviews.

Describe the review, evaluation and clearance of all records prior to the release of each lot of product. Include a description of the individual responsibilities of the manufacturing, quality and other appropriate units and procedures that detail how evidence of such review and clearance is documented. Describe procedures and specify the individual or unit responsible for verification that each section has been reviewed prior to release.

Question XV.E. How long are records kept?

Specify the retention period for all records pertaining to the manufacture of the products. Include the retention profile and a list of relevant SOPS for all records related to manufacturing and testing of each subject product.

Question XV.F. Describe the records used for distribution. How do these records allow for efficient recall?

Discuss the distribution record system with emphasis on traceability for recall purposes. Indicate special provisions or contractual arrangements for the distribution of product and refer to other sections of this form as appropriate.

Question XV.G. Describe the complaint file and adverse reaction reporting procedures.

Describe procedures for documenting and investigating all written and oral complaints regarding the product. Specify how and by whom complaints are reviewed and evaluated. Specify the site where these records are maintained. Complaints include product defect reports, complaints, and adverse reactions.

Question XV.H. Describe audit procedures and when and how trend analyses are performed.

Describe how often periodic audits of manufacturing and testing records are performed to evaluate the completeness and appropriateness of the records and the accompanying procedures. Indicate responsible personnel, how areas needing revision are identified and what actions are taken in response to audits. Describe the program for auditing of records in detail and include information on trend analyses, how and when such analyses are performed.

XVI. ADDITIONAL INFORMATION REQUIRED TO BE SUBMITTED

Question XVI.A. Please provide the following information: Question XVI.A.1. A description of the lot numbering system.

Describe how the lot number is assigned and the significance of any portion of the numbering system to include how lot numbers may evolve throughout the manufacturing process, how they are incorporated into the batch production and testing records and the significance of each element in the lot number.

Question XVI.A.2. An organizational chart.

Provide an organizational chart which illustrates the reporting authorities of the legal entity. It should describe the reporting responsibilities for manufacturing personnel in relation to the RH and the relationship of QC and QA in the reporting scheme. Provide assurance that the RH is in a position to be informed about manufacturing problems and/or changes and is in control of the establishment that is to be licensed in accordance with 21 CFR 600.10(a).

Question XVI.A.3. An environmental assessment report.

Submit an Environmental Assessment Report which is prepared in the format of 21 CFR Section 25.31(a). An Environmental Assessment describes the action that is being considered and should address all the components involved in the manufacture and disposal of the product. Discuss any request to utilize alternate formats with the CBER/Division of Establishment Licensing prior to filing the ELA/PLA.

Question XVI.A.4. Written agreements.

Provide written agreements outlining shared, divided, and/or contract manufacturing or testing in accordance with the cooperative manufacturing agreement policy (November 25, 1992 [57 FR 55544]). The degree of supervision and control exercised by the potential licensee should be evident in these agreements. Financial information may be purged from the documents. A guide to written agreements is appended to this document.

Question XVI.A.5. Curriculum Vitae for key manufacturing responsible personnel.

Provide the CVs for the RH, and for persons in charge of manufacturing, testing and QC departments. Do not include a CV for everyone involved in manufacturing or testing of the product.

Question XVI.A.6. An overview of the GMP training program.

Describe the Good Manufacturing Practices training program. Discuss the content and frequency of training as well as the credentials of those administering such training. Address all levels of 28 training, including on the job training and formal training programs. Discuss how such training is documented and how the program is audited or evaluated periodically.

XVII. COMMENTS

This section is provided for the applicant to provide any important information that may not have been included in any previous section.

XVIII. NAMES AND TITLES

Provide the names and signatures of the individuals responsible for overseeing the production and/or testing (those who report to the RH and are the first line supervisors for the areas). The RH signature certifies the truthfulness of the information in the application form and by such signature acknowledges his/her responsibilities under the regulations. Since biological products are also considered to be drugs or devices, this acknowledgment encompasses relevant portions of 21 CFR Parts 5, 1-99, 200-299, 300, 600-680 and 800-895.