USDA
United States Department of Agriculture

Animal and Plant Health Inspection Service

Veterinary Services

1400 Independence Ave, SW

Washington, DC 20250

VETERINARY SERVICES MEMORANDUM NO. 800.78

TO: Veterinary Services Executive Team
Directors, Center for Veterinary Biologics
Biologics Licensees, Permittees, and Applicants

FROM: Burke L. Healey
Deputy Administrator

ROSEMARY SIFFORD

Digitally signed by ROSEMARY SIFFORD
Date: 2019.09.24 10:07:21 -04'00'

SUBJECT: Preparation and Submission of Facilities Documents

I. PURPOSE

This memorandum provides guidance to firms on preparing and submitting facilities documents to the Animal and Plant Health Inspection Service (APHIS) in order to meet the intent of the regulations, as specified in title 9, *Code of Federal Regulations* (9 CFR), part 108, including the option of electronic submission of facility documents via the National Centers for Animal Health (NCAH) Portal. Facilities documents are one of the foundational requirements when applying for and maintaining a U.S. Veterinary Biologics Establishment License or U.S. Veterinary Biological Product Permit for Distribution and Sale.

II. CANCELLATION

This memorandum cancels Veterinary Services (VS) Memorandum No. 800.78 dated August 18, 2017.

III. BACKGROUND

Licensees and permittees should use the instructions provided by the regulations in 9 CFR 108 to prepare, revise, and submit facilities documents. The Center for Veterinary Biologics (CVB) uses these documents, if the documents are correctly drafted, to determine if the facilities' arrangement/design, functions described, and processes listed are adequate to allow for consistent preparation of product in accordance with the regulations and filed Outline of Production.

Licensees and permittees prepare veterinary biological products using various types of facilities, ranging from a single site and one building to multiple sites with many buildings per site. Facilities documents include the plot plan, the corresponding plot plan legend, the blueprint(s) and the corresponding blueprint legend(s), and any applicable appendices/addenda to the plot plan and/or blueprint legends.

Through a thorough review process, CVB-Inspection and Compliance (IC) assesses each facilities document submission to ensure firms prepare biological products in

facilities that meet the intent of the regulations, as outlined in 9 CFR 108. Examples of facilities document format are included as appendices to this memorandum.

IV. DEFINITIONS

A. Prepare or Preparation. Sometimes referred to as manufacture or produce; refers to the steps and procedures the firm uses in the manufacturing, processing, testing, packaging, labeling, and storing of a biological product, as described in 9 CFR 101.2.

B. Production Facility. A location on licensed premises or foreign manufacturing sites where the firm performs any step in preparing veterinary biological products.

C. Separate and Apart. A building or area on licensed premises that is physically and/or functionally distinct from the production facility, which the firm uses to effectively mitigate the possibility of cross-contaminating product from known and unknown sources.

If CVB considers a research facility/area to be separate and apart, CVB does not have to authorize the preparation of experimental biological products in that research facility/area, as described in 9 CFR 103.1.

CVB is implementing a similar practice for Quality Control (QC) areas that CVB considers to be separate and apart from the manufacturing area. For such QC areas, CVB will allow entities to continue to conduct serial release testing, but CVB will not require the entities to obtain CVB authorization to move experimental products, seeds, or cells into these areas for testing. The entity will be responsible for updating and submitting the list of fractions on an annual basis, or as requested by CVB, for these QC areas. CVB believes this new practice for QC areas should facilitate testing and may lead to a shorter submission time by the regulated entities in support of licensure.

D. Fraction. A specific antigen, its antibodies, or its antitoxin that constitutes a component of a biological product. For the purpose of facilities documents and 9 CFR 108, in addition to listing fractions, the firm should also list all live or inactivated organisms (whether or not they are used to prepare licensed product); DNA, RNA, or proteins prepared as a component of final product; and infected and non-infected cell lines. For the rest of this memorandum, all items listed above will be referred to as “fractions.” CVB does not consider completed product in sealed, final containers to be a fraction and does not require it to be listed for labeling and packaging areas.

E. Stationary Equipment. Equipment which the firm uses in the preparation of biological product (including testing) that is attached to the floor, wall, or ceiling of a room; that would require disassembly to remove from a room; or that would

require validation, certification, or calibration after it was moved and prior to use. Examples include, but are not limited to, autoclaves and lyophilizers built into a wall, hard-ducted biological safety cabinets, and equipment supporting air and water quality used in production areas, such as high-efficiency particulate air (HEPA) filter banks and water for injection systems.

F. Compartments**.** A controlled environment for which the firm uses air handling systems or other methods (such as a clean room) or specialized equipment (such as a laminar flow biosafety cabinet) to ensure protection of product and personnel and/or maintenance of adequate environmental conditions.

V. GENERAL GUIDANCE ON PREPARING FACILITIES DOCUMENTS

A. CVB requires that the firm include the following in facilities documents:

1. The establishment/permittee name and number, as shown on the U.S. Veterinary Biologics Establishment license or the U.S. Veterinary Biological Product Permit, on each page of the submission.

2. The address of the facility or premises the document(s) pertain to, clearly identified on each page of the submission. This is particularly important for establishments with multiple site locations.

3. Identification of the document on each page of the submission; e.g., 'Blueprint for Building 1, 1st Floor' or 'Addendum A – List of Fractions.'

4. A page number on each legend and addendum page. CVB does not require page numbers on plot plan and blueprint drawings and does not require firms to include cover pages and tables of contents with the firm's facilities document submissions.

5. The signature of a responsible firm official

a. Hardcopy submission, signature required on plot plans and blueprints. This should be the liaison or an alternate liaison designated for the entity.

b. NCAH Portal Submission, a signature is not required due to the credentials required to access the NCAH Portal.

6. Assurance that adequate water, lighting, and drains exist in all areas. This can be accomplished by a single statement in the plot plan legend or blueprint legend.

7. Legible documents.

   a. Hardcopy submission of plot plans and blueprints must be decipherable without the use of a magnifying glass. If needed, the plot plan and blueprint drawings may be on paper larger than standard size to ensure legibility.

   b. NCAH Portal Submission of plot plans and blueprints must also be legible. Scanned documents are not acceptable for electronic submission.

8. The scale used for electronic plot plans and blueprints should be supplied in such a way as to accurately reflect the size of the buildings. This can be accomplished several ways. Options include the following:

   a. Supply a scale based on the proposed drawing size. For example, the scale is based on a 8x11 sheet of paper.

   b. Bar measurements on the drawing that would enlarge or shrink with the drawing.

9. A 2-inch margin at the bottom of each document page to allow for the application of the VS file stamp.

B. Plot Plan and Plot Plan Legend

1. The firm must identify and include all buildings located on the licensed premises on the plot plan, even if they are not used in the preparation of biological products.

2. If aerial photographs are used as a plot plan submission, they must meet all the requirements for a plot plan as described in 9 CFR 108.3.

3. The firm's NCAH Portal Submission of the plot plan legend must be a pdf document generated from a word processing document. CVB will not accept scanned documents.

4. In the plot plan legend, the firm must list the function of each building shown on the plot plan. If a research or QC building is considered by CVB as separate and apart, the firm should clearly note the date of this approval in the plot plan legend as part of the description for the building function.

5. CVB allows the following addendums to be associated with the plot plan legend:

   a. For entities with multiple sites, a description of the movement of biological material between licensed premises and the precautions taken to maintain

proper storage conditions during transport. See VS Memorandum 800.87 for more information.

b. A list of the location and condition of records storage at alternate locations (off-licensed premises) when authorized by CVB. In accordance with 9 CFR 116.1(c), the firm is required to allow the inspection of these records by CVB. CVB may request these records for review during an on-site inspection. CVB provides additional guidance on electronic records stored at alternate locations in VS Memorandum 800.122.

c. The firm must list the name and address of the off-site storage for portions of master seeds and master cells. CVB provides additional information in VS Memorandum 800.113.

Include reference to the CVB mail log number and the date of the authorization letter in the addendum.

C. Blueprint

1. Even if only a portion of the floor is used for biological production, the firm should show the same level of detail for the entire floor. However, if the establishment provides adequate processes that mitigate adverse impacts to the preparation of veterinary biologics as a part of the facility document, CVB-IC may provide an exemption to 9 CFR 108.4(c). Then the entity would not need to show stationary equipment, sinks, drains, etc. on the blueprints for these non-biological process areas, but should list a general description regarding non-biological production area functions in the blueprint legend; e.g., preparation of veterinary pharmaceuticals.

2. The firm must identify all rooms shown on the blueprint by a letter or number that correlates with the identity of the room listed in the blueprint legend and at the establishment. This includes hallways, stairwells, closets, etc.

3. The firm must define all symbols and shapes on the blueprint; e.g., using a key on the blueprint or listed in the blueprint legend, and refrain from using those architectural-associated symbols or shapes which are inappropriate for blueprints submitted in accordance with 9 CFR 108.

4. The firm must show stationary equipment on the blueprint.

a. Firms may identify stationary equipment using the same identifier. For example, all autoclaves may be identified as “A” on the blueprints. The unique identification for each piece of equipment **should not** be included on the blueprint or listed in the blueprint legend.

The intended purpose of the equipment may impact the code given. For instance, CVB does not consider a laminar flow clean bench to be the same equipment as a biological safety cabinet, since they function in different ways and are used for different purposes. Therefore, the firm would give the laminar flow clean bench and biological safety cabinet two distinct identifiers on the blueprint.

c. Firms only need to show stationary equipment essential for the preparation of biological product. Displaying additional items (such as countertops, cabinets, shelves, etc.) might introduce unnecessary complexity to the submission.

d. Firms should not show equipment that is not considered stationary on the blueprint.

5. The firm must show water outlets (e.g., sinks and floor drains) for rooms in which product is exposed to the surroundings.

6. As an alternative to an addendum describing other precautions against cross-contamination, the firm may submit a separate blueprint showing clean room classification, air pressure differentials, and areas served by specific HVAC units. Similarly, the firm may have a separate blueprint to document the locations for personnel, equipment, and product movement.

D. Blueprint Legend

1. CVB will only accept a NCAH Portal Submission of the blueprint legend if it is a pdf document generated from a word processing document. CVB will not accept scanned documents.

2. The firm must identify all rooms, clearly state the function(s) of these rooms and avoid vague room function/use descriptions such as “laboratory,” “storage,” “production,” etc. For example, the the firm must provide a description of a production room which identifies what production steps occur in that room and must clearly identify the rooms used for both research and development (R&D) and licensed product preparation.

3. If CVB identifies a research or QC area(s) within a building as separate and apart, the firm must clearly document the date of CVB’s approval and the mail log number (if applicable) in the blueprint legend as part of the description for the room functions.

4. If CVB identifies a non-biological production area(s) described in the blueprint legend as separate and apart from biological production, then the firm is only required to provide a description of the room functions and may omit additional details which CVB would require for areas that are not separate and apart from biological production.

   An example is the manufacturing of pharmaceuticals in the same building as biologics. The firm lists the general function of the pharmaceutical production area and applicable room numbers in the blueprint legend as shown on the blueprint and describes the controls used to ensure biological product quality. See section V.C.1.

   Note: Biological production and non-biological production are not the same as licensed biological production and unlicensed biological production, respectively. If biologics produced under the Food and Drug Administration-Export Reform and Enhancement Act (FDA-EREA) and/or within R&D are prepared in the same building as licensed biologics, the firm is required to provide the same level of detail for all areas.

5. Firms must clearly identify rooms in which product and raw materials are exposed to the surroundings in the blueprint legend or on the blueprint itself in order for CVB to determine if the processes used to mitigate cross-contamination are adequate. This includes all rooms or compartments where product might be manipulated outside of a closed system.

6. The firm must identify stationary equipment located in the room in the blueprint legend, unless the items are sufficiently described on the blueprint, and list other essential (non-stationary) equipment used for product preparation within the room. CVB, in particular, requires that the firm clearly note if equipment produces aerosols, such as, but not limited to, sonicators and centrifuges.

7. The firm must clearly link any addendums associated with the blueprint legends to a specific room. The firm may place information that is repetitive across several rooms, such as lists of fractions or equipment and other precautions against cross contamination of product, etc., at the end of the blueprint legend as an addendum. The firm must provide a reference to one or more of these addendums for each applicable room listed in the blueprint legend, but the firm should not list or include standard operating procedures.

The firm must include the following, as applicable, in blueprint legend addendums :

a. *Methods used to Mitigate Contamination of Product*. This requirement is particularly applicable to the processes used in rooms in which product or raw materials are exposed to the surroundings.

(1) Decontamination procedures. The firm must use cleaning and disinfection methods that CVB accepts as appropriate for the fractions used and the processes performed, and the firm must:

Identify the disinfectant by chemical type and not just by the trade name. CVB uses this information to determine the antimicrobial properties. Document the frequency of the process in specific terms. For example, CVB might accept "as needed, but at least after every use" as adequate, but CVB will not accept terms that do not provide sufficient information to determine the appropriateness of the process, such as "as needed" or "on a routine basis."

(2) Other precautions against cross contamination. The firm must use essential processes, as determined by CVB, beyond the decontamination procedures to mitigate contamination of the product. The firm must include the following items, as applicable, in a blueprint legend addendum:

- Entry and exit procedures for personnel, equipment, and materials. For example, gowning procedures within an area remotely located from a production room; e.g., changing into scrubs upon entry into a production building
- Room/Area access
- Campaign manufacturing. Defined as working with only one fraction at a time within a production room
- Environmental monitoring
- Clean room classification, room air pressure differentials, and dedicated HVAC units with HEPA filtered air supply and/or exhaust shown on a blueprint drawing
- Personnel, equipment, and product movement (may be shown on a blueprint drawing)
- Drainage and plumbing systems. Function to prevent effluent backflow into critical production rooms. Drainage lines can be decontaminated

b. *Fractions List(s)*. See section IV.D.

(1) CVB considers all fractions, including, but not limited to, bacterial, viral, fungal, parasitic, and prion agent fractions listed in the facility documents to be live agents, unless the firm clearly states otherwise.

(2) Include only those fractions routinely prepared in a room at the facility for which the documents are being submitted. CVB prefers that the firm refrain from listing any and all fractions that may ever possibly be used in a room. CVB requires the firm to update the fraction listing on a regular basis; however, CVB does not require immediate updating of the fraction listing whenever a new fraction is obtained.

(3) For QC and R&D rooms, the firm may have a broader list of fractions.

(4) The firm should not refer to fractions as "approved." The purpose for listing fractions in the facilities document is to provide information that CVB uses to determine if the facilities, equipment, and processes are appropriate to mitigate contamination, not to confirm the CVB-Policy, Evaluation, and Licensing's authorization to introduce an organism into the production facility.

(5) The firm cannot simply list fractions in the facilities documents in lieu of completing the CVB-required process to request permission to prepare experimental biological product in a production facility in accordance with 9 CFR 103.1.

c. *Exemptions to 9 CFR 109, Sterilization of Equipment*

(1) The firm must not use sterilization methods other than those listed in 9 CFR 109.1 for containers, instruments, and equipment that come into contact with product, unless CVB has granted an exemption for the firm to use these methods. The exemption listing should include the following:

- Listing of containers, instruments, and/or equipment
- Method of sterilization/sanitation used
  - Time
  - Temperatures
  - Exposure ranges; e.g., irradiation processes reported in kilograys or other validated assurance levels
  - Sanitation methods; e.g., fractionation columns
- The firm must provide a statement indicating records supporting verification/validation of the method are on file at the establishment.

Depending on the proposed sterilization method, CVB may request additional information.

- System of recordkeeping for the alternative method

(2) The firm shall equip steam and dry-heat sterilizers with automatic recording gauges. CVB requires an exemption to 9 CFR 109.2 if a firm has older equipment or smaller equipment that does not have automatic recording gauges. In the exemption listing, the firm must include the alternative method of recordkeeping for critical parameters required for sterilization.

8. In order to minimize the number of pages in a blueprint legend submission, CVB prefers the firm to maximize the information listed per page and avoid partially blank pages resulting from listing only one room per page.

E. Revision of Facilities Documents

1. Facilities documents should be reviewed on a regular basis (e.g., annually) and revised when changes occur to the facilities and/or procedures described in the facilities documents that may impact the preparation of licensed product. This includes additions to or deletions from the 'Fractions' list.

2. A summary of changes

a. For hardcopy submissions, CVB requires the firm to provide a summary of changes with each revision of facilities documents.

b. For NCAH Portal Submissions, CVB requires the firm to provide a summary of changes for:

(1) Each plot plan and blueprint, including a list of changes made and why for major construction changes.

(2) The first electronic submission of the legends and addenda. Subsequent updates submitted electronically no longer require summary of changes.

c. CVB recommends, but does not require, that the firm place a supersedes date on each page.

F. Preliminary Documents

Licensees, permittees, and applicants may submit preliminary drawings for comment before construction of new facilities, when the company anticipates renovation of existing facilities, or when other facility changes will affect workflow. CVB will file, rather than approve, the preliminary facilities documents and will maintain them for future reference. CVB may require an inspection of new construction or renovation of facilities prior to product preparation in these areas.

G. Submission of Facilities Documents

1. Hard Copy

a. Prior to submission, personnel familiar with the regulations and guidance documents pertaining to facility documents should review the submission for adequacy and completion. This is a critical step in reducing the amount of preparation and review time required by both the firm and CVB.

b. CVB will stamp acceptable submissions as filed. CVB will return one stamped copy to the submitter and file one copy. CVB may return facilities document submissions requiring revision as unprocessed, with a request for the licensed, permitted, or applying establishment to resubmit the documents to CVB after the necessary revisions have been made.

c. Licensees and permittees should submit two copies of the facilities documents to the Center for Veterinary Biologics-Inspection and Compliance, 1920 Dayton Avenue, P.O. Box 844, Ames, IA 50010.

d. If it is submitting more than two copies of the facilities documents, the firm should explain why this is necessary in a cover letter.

2. NCAH Portal Submissions

a. Prior to submission, personnel familiar with the regulations and guidance documents pertaining to facility documents should review the submission for adequacy and completion. This is a critical step in reducing the amount of preparation and review time required by both the firm and CVB.

b. CVB will stamp acceptable submissions as filed. CVB may include a request for revisions with the stamped facility documents; CVB expects these revisions to be addressed at the manufacturer's next annual review.

c. Licensees and permittees should follow NCAH Portal User Guides 9 and 26 when submitting facility documents electronically. NCAH Portal User Guides are available on the CVB website.

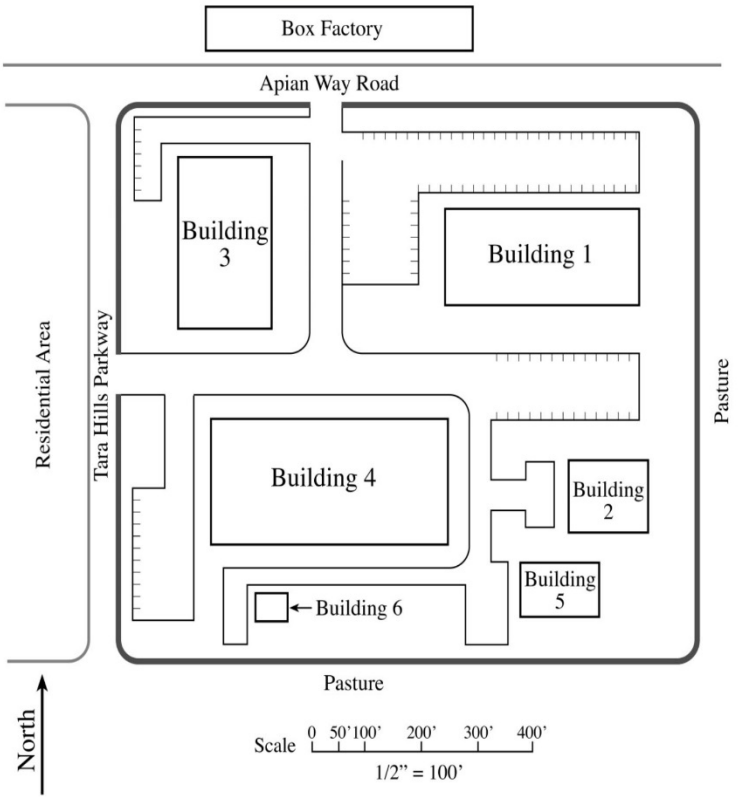
H. Examples of Facilities Documents

There are examples for each type of facility document typically found in a complete facilities document submission in the appendices to this memorandum. CVB intends for these examples to be used in conjunction with the regulations listed in 9 CFR 108 and guidance in VS Memorandum 800.78. CVB does not intend for these examples to address all of the requirements associated with preparing facilities documents or to be templates.

Appendices

Pursuant to the Congressional Review Act (5 U.S.C. § 801 et seq.), the Office of Information and Regulatory Affairs designated this rule as a non-major rule, as defined by 5 U.S.C. § 804(2).

Appendix I: Plot Plan (example)



Plot Plan
Establishment XYZ
Best Biologics
1234 Coastal Highway
Anywhere, Texas 92510

I.M. Liaison
Signature of Liasion
May 28, 2015
Date of Preparation

Boundary of Licensed Premises

Note: The content of this appendix does not constitute endorsement by APHIS of the facilities methods, or procedures represented in this example

Leave a 2-inch margin at the bottom of the page to allow for the Veterinary Services file stamp.

Appendix II: Plot Plan Legend (example)

Page 1

Best Biologics
Establishment 2468

1234 Coastal Highway
Anywhere, Texas

Building 1
Function: Preparation of viral veterinary biological products.
Construction Materials: Steel frame with exterior walls composed of concrete panels with a metal roof. Interior walls are epoxy painted concrete block or drywall or fiberglass reinforced paneling. Ceilings are epoxy-painted drywall. Floors are poured epoxy over concrete.

Building 2
Function: Small animal building used for QC testing of veterinary biological products.
Construction Materials: Steel frame with exterior walls composed of concrete panels with a metal roof. Interior walls are epoxy paint over concrete block. Ceilings are epoxy-painted drywall. Floors are poured epoxy over concrete.

Note: This building is considered separate and apart from production. See the CVB authorization letter dated January 22, 2017 (ML 123456).

Building 3
Function: Administrative Offices (records regarding the preparation of licensed product are maintained here).

Building 4
Function: Preparation of bacterial veterinary biological products, QC testing, and R&D.
Construction Materials: Steel frame with exterior walls composed of concrete panels with a metal roof. Interior walls are epoxy-painted concrete block or drywall or fiberglass reinforced paneling. Ceilings are epoxy-painted drywall. Floors are poured epoxy over concrete.

Building 5
Function: Warehouse, packaging and labeling
Construction Materials: Steel frame with metal siding and a metal roof. Interior walls and ceilings are epoxy-painted drywall. Floors are sealed concrete.

Leave a 2-inch margin at the bottom of the page to allow for the VS file stamp.

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Appendix II (continued)**: Plot Plan Legend (example)**

Best Biologics
Establishment 2468

1234 Coastal Highway
Anywhere, Texas

Building 6
Function: Maintenance Shop

Water, Drainage, and Lighting – Adequate water, drains, and lighting exist in all rooms* used in the preparation of veterinary biological product.

*Some rooms do not require water and/or drains.

Examples of buildings requiring blueprints:
Manufacturing
Shipping – Distribution
Testing, including animal facilities

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Appendix III: Plot Plan Legend, Addendum 1
Storage of Master Seed Off Licensed Premises (example)

Best Biologics
Establishment 2468

1234 Coastal Highway
Anywhere, Texas

In addition to the master seed organisms stored on Best Biologics licensed premises, additional quantities of these master seed organisms will be stored at the following:

A-1 Cold Storage
5678 Mountain Top Road
Somewhere, Colorado
Telephone: 777-888-9999

The management at A-1 storage has provided Best Biologics with written assurance that this off-site location may be inspected by APHIS inspectors. See the CVB authorization letter dated January 22, 2017 (ML 000000).

Leave a 2-inch margin at the bottom of the page to allow for the VS file stamp.

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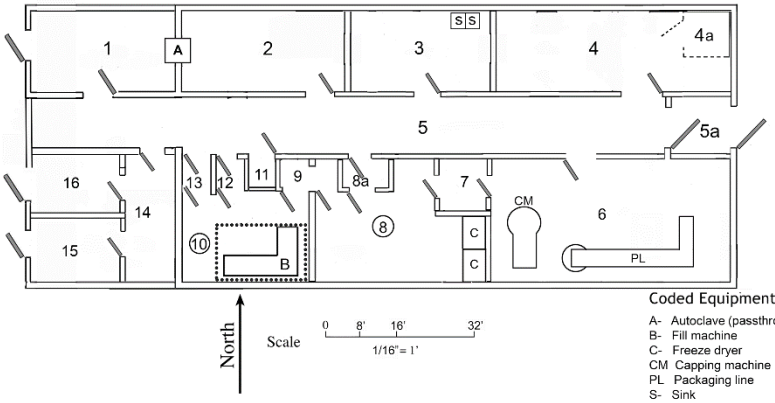
Appendix IV: Blueprint - Building 1, Viral Suite (example)*

* For illustration purposes, this example only shows a portion of the production area, not the entire Building 1 floorspace. The expectation would be to have the entire floor of the building shown on the blueprint.



Blueprint - Building 1
Establishment 2468
Best Biologics
1234 Coastal Highway
Anywhere, Texas 92510

J.M. Liaison
Signature of Liaison
May 28, 2015
Date of Preparation

Coded Equipment to list in Blueprint Legend

A- Autoclave (passthrough)
B- Fill machine
C- Freeze dryer
CM Capping machine
PL Packaging line
S- Sink
- - - - Cage (secured)
•••••• Clean room

(1) Room number inside a circle indicates product is exposed to the surroundings.

Note: The content of this appendix does not constitute endorsement by APHIS of the facilities methods, or procedures represented in this example

Leave a 2-inch margin at the bottom of the page to allow for the Veterinary Services file stamp.

Appendix V: Blueprint Legend - Building 1, Viral Suite (example)*

* For illustration purposes this example only describes a portion of the production area, not the entire Building 1 floor. The expectation would be to have a description of the entire floor in the actual blueprint legend.

Best Biologics
Establishment 2468

1234 Coastal Highway
Anywhere, Texas

Room 1
Function: Material & Supply Entry
Equipment:
Coded Stationary Equipment: Autoclave (A)
Fractions: NA
Room Management: Addendum B, Section I

Room 2
Function: Storage for Clean/Sterile Production Equipment & Supplies
Equipment:
Coded Stationary Equipment: Autoclave (A)
Non-stationary equipment: filling equipment, lyophilizer trays & racks
Fractions: NA
Room Management: NA

Room 3
Function: Production Equipment Cleaning and Preparation
Equipment:
Coded Stationary Equipment: Double bin sink (S)
Fractions: NA
Room Management: Addendum B, Section I

Room 4
Function: Walk-in Cooler – Storage of Completed Product in Bulk and Final Container
Equipment:
Non-stationary equipment: Fill tanks
Fractions: See Addendum A, Section A
Room Management: NA

Leave a 2-inch margin at the bottom of the page to allow for the VS file stamp.

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Appendix V (continued)**: Blueprint Legend - Building 1, Viral Suite (example)**

Best Biologics
Establishment 2468

1234 Coastal Highway
Anywhere, Texas

Room 4a
Function: Storage of APHIS Retention & QC Samples
Equipment: NA
Fractions: NA
Room Management: Chain link enclosure with secure entry

Room 5
Function: Hallway
Equipment: NA
Fractions: NA
Room Management: NA

Room 5a
Function: Product, Equipment, Material Airlock
Equipment: NA
Fractions: NA
Room Management: NA

Room 6
Function: Capping, Packaging, and Labeling of Lyophilized Product
Equipment:
Coded stationary equipment – Packaging/Labeling Line (Z); Capping machine (CM)
Non-stationary equipment – Portable and secure label storage cages; product transfer carts
Fractions: NA
Room Management: Addendum B, Section I

Room 7
Function: Product Transfer Airlock
Equipment: NA
Fractions: NA
Room Management: Addendum B, Section I

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Appendix V (continued)**: Blueprint Legend - Building 1, Viral Suite (example)**

Best Biologics
Establishment 2468

1234 Coastal Highway
Anywhere, Texas

Room 8
Function: Lyophilization of Viral Products
Equipment:
Coded stationary equipment – Freeze Dryers (C)
Non-stationary equipment – Trays and racks for loading and transporting vials to be freeze dried; hand seal crimper
Fractions: See Addendum A, Section A
Room Management: Addendum B, Sections II & III

Room 8a
Function: Personnel Airlock
Equipment: NA
Fractions: NA
Room Management: Addendum B, Section I; Addendum C, Section II

Room 9
Function: Product Transfer Airlock
Equipment: NA
Fractions: NA
Room Management: Addendum B, Sections II (a-c) & III

Room 10
Function: Fill Room for Lyophilized Viral Products
Equipment:
Coded Stationary Equipment – Fill machine (B), Clean room (…)
Non-stationary equipment – Table top scale, transport rack for vials, intermediate-fill tank
Fractions: See Addendum A, Section A
Room Management: See Addendum B, Sections II & III; Addendum C, Section III

Leave a 2-inch margin at the bottom of the page to allow for the VS file stamp.

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Appendix V (continued)**: Blueprint Legend - Building 1, Viral Suite (example)**

Best Biologics
Establishment 2468

1234 Coastal Highway
Anywhere, Texas

Room 11
Function: Fill Tank Room
Equipment:
Non-stationary equipment: Fill tank
Fractions: See Addendum A, Section A
Room Management: Addendum B, Section I

Room 12
Function: Equipment and Supply Airlock
Equipment: NA
Fractions: NA
Room Management: Addendum B, Section I

Room 13
Function: Personnel Airlock
Equipment: NA
Fractions: NA
Room Management: Addendum B, Section I; Addendum C, Section III.a

Room 14
Function: Viral Production Primary Personnel Airlock
Equipment: NA
Fractions: NA
Room Management: Addendum B, Section I

Room 15
Function: Women's Locker Room/Rest Room
Equipment: NA
Fractions: NA
Room Management: Addendum C, Section I

Room 16
Function: Men's Locker Room/Rest Room
Equipment: NA
Fractions: NA
Room Management: Addendum C, Section I

Leave a 2-inch margin at the bottom of the page to allow for the VS file stamp.
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Appendix VI: Blueprint Legend - Building 1, Addendum A
Listing of Fractions (example)

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A. Viral Fractions

Bovine Rhinotracheitis Virus
Bovine Respiratory Syncytial Virus
Parainfluenza$_3$ Virus
Canine Distemper Virus
Canine Parvovirus
Canine Coronavirus
Equine Herpesvirus, Type 3
Equine Herpesvirus, Type 4
Equine Influenza Virus
West Nile Virus

B. Bacterial Fractions

Actinobacillus pleuropneumoniae
Bordetella bronchiseptica
Mannheimia haemolytica
Pasteurella multocida
Campylobacter fetus
Clostridium chauvoei
Clostridium septicum
Haemophilus somnus
Haemophilus parasuis
Leptospira canicola
Leptospira hardjo
Leptospira icterohaemorrhagiae
Leptospira pomona

C. Production Cell Lines

Madin-Darby Bovine Kidney
Dog Kidney
Vero

D. Organisms for Quality Control Use Only

Bacillus subtilis
Candida albicans

Leave a 2-inch margin at the bottom of the page to allow for the VS file stamp.

Note: The content of this Appendix does not constitute endorsement by APHIS of the facilities, methods, or procedures represented in this example.

Appendix VII: Blueprint Legend - Building 1, Addendum B
Viral Suite - Decontamination Procedures (example)

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Section I. Applicable to all production areas:

a. Floors are mopped with a phenolic disinfectant solution at the end of each shift/daily.
b. Walls are cleaned with a phenolic disinfectant solution weekly.
c. Ceilings are cleaned with a phenolic disinfectant solution quarterly.
d. Room 1 only - Items entering into Room 1 are steam sterilized or are sprayed with a phenolic disinfectant solution and held for 20 minutes prior to exiting the room.
e. Room 6 only - The capping machine and packaging line are cleaned with sodium hypochlorite disinfectant wipes after each serial is sealed/packaged.

Section II. Applicable to production rooms in which product is exposed to the surroundings:

a. All work surfaces, including biological safety cabinet, are cleaned after each operation with 70% Isopropyl alcohol.
b. Floors are cleaned after each operation with a phenolic disinfectant solution.
c. Walls and ceilings are cleaned with a phenolic disinfectant solution weekly.
d. Equipment, containers, instruments, and materials are placed in the airlock for the room and sprayed with a phenolic disinfectant solution and held for 20 minutes prior to moving into and or out of the production room.

Section III. Movement of equipment and material from rooms where product is exposed to the surroundings:

a. Removable equipment items are bagged and sprayed with 70% Isopropyl alcohol.
b. Waste is double bagged and the outer bag is sprayed with 70% Isopropyl alcohol prior to exiting the room.
c. Contaminated waste is chemically sterilized or disinfected prior to final disposal.
d. Room 8 only: Lyophilizer –Vial trays and lyophilizer shelves are wiped with a phenolic disinfectant solution. A steam-in-place (SIP) procedure is performed on the inside of each lyophilizer unit after each serial is freeze dried.
e. Room 10 only: Fill line – Removable parts are cleaned and steam sterilized. The rest of the line and associated clean room is wiped with a phenolic disinfectant solution prior to and after each serial is filled.

Disinfectants used include: sodium hypochlorite, phenolic agents, 70% Isopropyl alcohol, and peracetic/acetic acid hydrogen peroxide. Sodium hypochlorite disinfectant wipes may also be used for surfaces.

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Appendix VIII: Blueprint Legend - Building 1, Addendum C
Viral Suite - Other Precautions Against Cross Contamination (example)

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Section I. Applicable to Building 1 Entry:

a. Access to the Viral Suite is limited to authorized personnel.
b. Employees and visitors change into scrubs, put on a bouffant cap, beard cover (if applicable), safety glasses, and shoe covers. Hands are washed and a sanitizing foam is used.

Section II. Additional precautions taken for working in Lyophilization Room 8:
Secondary gowning occurs prior to entry into Room 8, which includes donning a lab coat, surgical mask, gloves, and shoe covers. Secondary gowning is removed and hands are washed and/or hand sanitizer is used prior to exiting the production room.

Section III. Additional precautions taken for working in Fill Room 10 and Clean Room 10a.

a. Full body sterile suit including gown, hood, and booties; mask; two pairs of gloves, and safety glasses are donned prior to entry into Room 10. Secondary gowning is removed and hands are washed and/or hand sanitizer is used prior to exiting the Production Room.
b. Open manipulation of product is performed inside a positive pressure HEPA-filtered Clean Room.
c. Environmental monitoring is performed during filling with alert and alarm levels determined to demonstrate effectiveness of processes to mitigate cross-contamination of product. Media fills are performed quarterly.

Section IV. Additional precautions against cross contamination may be shown using a specialized blueprint drawing such as Appendix IX – Building 1 HVAC/Airflow Blueprint.

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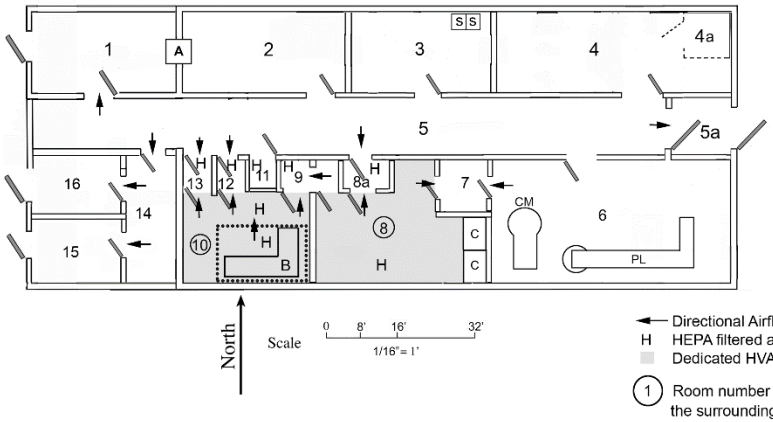
Appendix IX: Building 1- HVAC/Airflow Blueprint (example)*

* For illustration purposes, this example only shows a portion of the production area, not the entire Building 1 floorspace. The expectation would be to have the entire floor of the building shown on the blueprint.



Blueprint - Building 1
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J.M. Liaison
Signature of Liaison
May 28, 2015
Date of Preparation

← Directional Airflow
H HEPA filtered air supply
Dedicated HVAC

(1) Room number inside a circle indicates product is exposed to the surroundings.

Note: The content of this appendix does not constitute endorsement by APHIS of the facilities methods, or procedures represented in this example

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Appendix X: Blueprint Legend - Building 1, Addendum D Viral Suite - Items Exempted from the Requirements of 9 CFR 109.1 and/or 109.2 (example)

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The following equipment is exempted from the sterilization requirements in 9 CFR 109.1:

I. Glass vials used for bottling final product

A. Method of Sterilization

Vaccine bottles are sterilized by gamma irradiation at 30 kGy by the supplier.

B. Documentation

1. Certificate of sterility provided by the supplier is maintained by Quality Assurance.

2. Each production record contains the lot number for the bottles used in serial preparation.

II. Rubber stoppers for vials of product

A. Method of Sterilization

Rubber stoppers are sterilized by gamma irradiation at 30 kGy by the supplier.

B. Documentation

1. Certificate of sterility provided by the supplier is maintained by Quality Assurance.

2. Each production record contains the lot number for the stoppers used in serial preparation.

Records supporting verification/validation of the sterilization method described above are on file.

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Appendix X (continued)**: Blueprint Legend - Building 1, Addendum D**
Viral Suite - Items Exempted from the Requirements of
9 CFR 109.1 and/or 109.2 (example)

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The following equipment is exempted from the sterilizer recordkeeping system requirements specified in 9 CFR 109.2:

Stainless Steel Fill Tanks

A. Method of Sterilization

Tanks are steam sterilized in place (SIP) through a steam line in Room 4 for a minimum of 90 minutes at 121 ºC. Temperature is verified visually by using a calibrated in-tank thermometer. Once 121 ºC is achieved, this is the start time. Temperature readings are taken every 15 minutes with a final reading taken at 90 minutes.

B. Documentation

All SIP time and temperature readings are recorded in the SIP log in Room 4. The operator confirms the run time and temperature of the SIP for the tank along with the SIP run number in the appropriate space on the tank tag. The tag is subsequently placed into the production record. All records are authenticated and dated.

Signed:

_____

Date:

_____

Printed name and title:

_____

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