Facility Documents: Specialist Review and Outgoing Correspondence

BACKGROUND: The main objective in the Specialist's review and assessment of facility document submissions is to determine if the facility construction and arrangement, along with the established processes and procedures regarding preparation of licensed or permitted biological product, appear to effectively work together to ensure consistent manufacturing of products and to mitigate contamination of licensed or permitted product. The Specialist should become familiar with both title 9, *Code of Federal Regulations* (9 CFR), part 108, and the most current version of Veterinary Services (VS) Memorandum 800.78 in order to conduct a meaningful review.

SPECIALIST REVIEW (SECONDARY DOCUMENT REVIEW)

Below is a listing of some of the items each Specialist should consider when reviewing facility documents. Keep in mind that depending on the type of licensed/permitted product prepared at the facility, and processes and procedures established to mitigate cross contamination of product will likely differ significantly. For example, licensed establishments preparing injectable vaccines will likely have established more safeguards to protect product against cross-contamination than the manufacturer of diagnostic test kits which do not require final sterility testing. In performing your review ask yourself the question – *Does the facility appear appropriate for the intended activities and use as described in the filed Outline(s) of Production?*

<u>FACILITY DOCUMENT SUBMISSION TYPE</u>

New Address – sites not currently included on the establishment license
Prelicensing – self explanatory

1. Licensee – Has an APHIS Form 2001 been submitted to Policy, Evaluation, and Licensing (PEL)?

2. Permittee – Has an APHIS Form 2005 or a special outline been submitted?

3. Diluent – not technically required, but is site listed in a special outline?

4. Does the site require an inspection prior to adding it to the establishment license?
    a. Prelicensing – Requires an inspection
    b. New Address for Production – requires an inspection unless there are extenuating circumstances (rare)
    c. New Address for Testing or Distribution – depends, but can be approved without an inspection. There must be a statement from the firm indicating the personnel are trained (if new to the process) and equipment is adequate to provide similar results. May require technology transfer with testing by CVB.

New Building – new construction on a site listed on the establishment license
Remodeled Facility – construction which moves walls, areas, or an addition

Does the building require an inspection prior to filing the facility documents?

1. Production – YES
   Requires an inspection unless there are extenuating circumstances (rare).
   a. New or remodeled facilities can be used AT RISK prior to an inspection.
   b. Product made in a new or remodeled facility IS NOT eligible for consideration for marketing prior to assessment of the facility, equipment, personnel, and processes. Samples and APHIS Form 2008s should be held until after the inspection results are documented.
   c. Equipment and processes should be validated prior to an inspection.

2. Testing, Distribution – depends, but can be approved without an inspection as long as the personnel, equipment, and processes are the same.

Revision – usually due to an update from the firm or inspection findings.

REVIEW PROCESS

1. Process facility documents in the order in which they are received in your queue. Exceptions will arise based on program priorities.

2. Review the **ICFRM0018** and/or **ICFRM0019** (BCA Preliminary Review of Facility Documents) attached to the Mail Log as the document type of "Internally Routed." Pay special attention to any comments made on these sheets. Check to see if the Biologics Compliance Assistant (BCA) previously sent the documents back unprocessed (BCAs have the authority to send back incomplete documents after their initial review.) and if so, were the proper corrections made? Depending on the BCA's concern(s) noted on either I**CFRM0018** and/or **ICFRM0019**, you may need to identify the item(s) of concern noted on these forms on **ICTEM0045**, *Facility Document Correspondence*.

3. Review the Specialist's response to the facility documents submitted immediately prior to the submission currently under review to see if the firm has addressed all of the concerns previously raised. If it is determined through your review that the overall quality of the submission is poor and/or the firm has not addressed issues needing correction as stated in the previous facility document correspondence, then the submitted documents may be returned unfiled along with the completed **ICTEM0045** form. In addition, communicate to the firm that compliance action may be taken if the next facility document submission does not provide complete and accurate information.

4. If there is to be a compliance action based on the facility document submission, reference the date of the previous 'blueprint' letter(s) sent to the firm. The firm may be in violation of 9 CFR 114.1 if they have not addressed previous CVB requests to make revisions to one or more of the facility documents.

5. The supersedes date **does not** need to be applied to or assessed for correctness for each document page. Versioning of the documents is encouraged, but not required. If the supersedes dates are provided, you do not need to check these against the filed facility documents.

6. Compare the summary of changes to the documents submitted. The two should be in agreement. If not, then contact the firm for clarification and/or return the documents unprocessed.

7. We will no longer be making pen-and-ink changes to the documents. Instead, make note of items needing revision in your response back to the firm. **Rule of thumb**, if it was acceptable for a pen and ink change, most likely it is appropriate to request a revision rather than send back unfiled.

DOCUMENTATION OF REVIEW

1. Center for Veterinary Biologics Inspection and Compliance Facility Document Submission Worksheet. This form is currently under review by OMB and will be referred to as Facility Document Submission form or FDS.
   a. Complete the bottom portion of the FDS form by checking one or more of the three boxes in Block 9, CVB Action.
      Box 9.A - Documents Filed
      Box 9.B - Documents Filed, Revisions Requested
      Box 9.C - Documents Returned
   b. Sign the form in Block 10.A. Leave Block 10.B blank as this is the date the documents are stamped/sent back to the firm. This date will be filled in by the BCA performing the final processing of the submission.

2. Facility Document Correspondence, **ICTEM0045**
   a. Documents Filed, no revisions or changes needed – Mark Box 9, no need to use **ICTEM0045**
   b. Documents Filed, Revisions Requested – documents may be complete but lack clarity – Mark Box 9.B, and;
      i. List areas or examples of areas in need of revision on **ICTEM0045***
      ii. No timeframe is associated with these revisions, but normally it would be expected to be revised at next review, no later than annually.
      iii. Upload **ICTEM0045** response as "Internally Routed"
   c. Documents Returned – the quality of the submission is poor or significant requirements have not been met and all of the documents are being returned without filing – Mark Box 9.C, and;
      i. The entire submission is sent back, none of it is filed with CVB.
      ii. The entire submission does not need to be reviewed. Once it has been determined the documents lack a quality review, the Specialist may reject the submission

without further resources used. List areas or examples of areas in need of revision on **ICTEM0045.**

iii. A timeframe for resubmission is listed. Suggest 30 or 60 days.

iv. Tag mail item "Returned Unprocessed". Use only when all of the documents go back "unprocessed."

v. Upload **ICTEM0045** response as "Internally Routed"

d. Documents Filed, Revisions Requested and Documents Returned without filing – Mark Boxes 9.B and 9.C. **See example A below**.
Upload **ICTEM0045** response as "Internally Routed"

*General Guidance for completing **ICTEM0045**:

i. Include establishment name, number, and site of the submission in the header of the template.

ii. List information for each document under that document listed in the template box, including document identification (building number/letter and floor, if applicable)

BLUEPRINT – Building 1

iii. Include the items noted during the BCA review of the documents. This is NOT applicable if the submission is being returned based only on the preliminary review by the BCAs.

iv. Each issue will be uniquely identified by a number, starting with 1.

v. Clearly state the error or omission in the facility document.

vi. Include the 9 CFR violation with each issue. See template for formatting.

Example A

Good Stuff Biologics, Est.999
Ames, Iowa

Facility Documents Filed – Revisions Requested

Review VS Memorandum 800.78, Preparation and Submission of Facilities Documents, for established practices related to preparing facility documents. All corrections required may not be listed. Address all revisions requested and ensure the submission has been reviewed by personnel familiar with the regulations and guidance documents prior to resubmission.

Blueprint Legend – Building 1

1. Do not use tradename when listing disinfectants used, list by active ingredient(s) [Reference: 9 CFR 108.5(b)(1)]

Facility Documents Returned – Resubmit with Corrections by December 15, 2017

This part of the submission was not adequate or complete and did not meet the regulations cited in 9 CFR Part 108. All corrections required may not be listed,

Blueprint – Building 1

2. Compass point was not shown.
[Reference: 9 CFR 108.4(h)]

3. Move Mail Log on to Section Leader Review (IC) – William Huls. Renee Schnurr will act as back-up.

ITEMS TO CONSIDER WHEN REVIEWING THE FACILITY DOCUMENTS

1. Determine if there is adequate **separation of production areas** from non-production areas. **ICWI0004**, *General Guidelines on Designating a Building or Area Separate and Apart*, may apply in making this determination.

2. Does the level of control regarding mitigation of cross contamination appear appropriate for the product(s) prepared? Line clearance procedures performed in between production runs may be the primary focus for firms that manufacture diagnostic tests, where as many safeguards against cross contamination of licensed product should be established for injectable vaccines.

3. In areas **where product is exposed** to the surroundings, is it clear whether manipulations occur inside or outside of a compartment? For example, this should be obvious in a fill suite but what about other areas, such as blending? The documents should state where product is exposed to the surroundings and therefore, there should be a higher degree of scrutiny in our review of these areas regarding the firm's description of how cross contamination is mitigated.

4. Look at any potential negative impact R&D activities may have on licensed/permitted product. For example, sharing of equipment, positioning of R&D to product preparation areas, and so forth. Is the listing of Exemptions to 9 CFR 109.1 and 109.2 adequate to address concerns here?

5. Is the air handling system adequate in areas where product is exposed to the surroundings for the functions performed? Assess **directional airflow** (e.g., air flowing into or out of a fill suite) and air **filtration** (HEPA filters) for the air supplying production rooms and

compartments to make this determination. Some questions to consider are: Is air re-circulated within a room, and what is the turn-over rate per unit time? Do some rooms have a dedicated air supply? Is backflow prevention necessary and if so, is it in-place?

6. In assessing traffic patterns, determine how **personnel** and **materials** enter into and exit out of production rooms.

7. Ensure **room function(s) are spelled out** clearly in the blueprint legend or in an addendum to this legend (e.g., methods to mitigate cross-contamination – airlock function, clothes change). Often times, the room function supplied by the firm is more like a room name. Providing an adequate description of the room function(s) is key in determining if methods to mitigate cross contamination are appropriate.

8. We have explained in the most recent VS Memorandum 800.78 what the firm should list as equipment; however, if a document comes in with toilets shown, for example, do not consider this as an issue in determining to accept or reject the documents. If there are blatant errors regarding stationary equipment identified on the blueprint or corresponding legend, inform the firm. The documents may be sent back unfiled or result in a request for revisions.

9. If a floor drain or sink is located in a production room, do the documents describe any backflow prevention in the drain lines to prevent the possibility of effluent draining into the room?

This is by no means an all-inclusive list of items to consider in reviewing facility document submissions. If you have a question regarding the review that cannot be found or is not clear in 9 CFR 108 or VS Memorandum 800.78, then don't hesitate to discuss the issue with the Facilities Manager or IC Section Leader.