CVB – IC Policy and Procedures when the Licensee/Permittee has been Granted an Animal Safety Testing Exemption Under VS Memo 800.116

Background

An Outline of Production shall be on file with Animal and Plant Health Inspection Service for each licensed biological product or for each biological product authorized to be imported into the United States for Distribution and Sale. Preparation of a biological product in a licensed establishment, or a foreign manufacturing site in regard to permitted product, shall be in accordance with the Outline of Production, and any associated Special Outline(s) for such product filed with Animal and Plant Health Inspection Service.

Licensed biological products shall be prepared as required by the regulations and in accordance with a filed Outline of Production as prescribed in §§114.8 and 114.9. No change shall be made in the preparation of a biological product without prior approval of the Administrator. Outlines and Special Outlines of Production shall be reviewed at least once a year by the licensee/permittee for accuracy and sufficiency as stipulated by 9 CFR 114.8(d).

The PEL Reviewer Manual, Work Instruction (WI) 4.5.1, *Animal Safety Testing Exemption*, issue date 02Jan14, describes the PEL process for approval of the exemption.

A. Changes to the Outline of Production

The PEL Review Manual, WI 4.5.1, indicates that the licensee/permittee should have:

1. Added the date the exemption was approved to the Outline of Production.

2. The safety tests that the firm should perform if the exemption is suspended for any reason should remain in the Outline of Production.

3. Section V.A. Sterility Testing must be conducted in accordance with 9 CFR 113.26 for all products. (No positive test vessels)
   - For oral antibody products; identification of contaminants is also required.
   - The approval date of dilution of preservative studies must be provided in Section V.A.
   - Media used in sterility testing should be validated for growth promotion as per 9 CFR 113.25(b) or an approved exemption should be documented in the Outline of Production.

4. The Outline of Production must include methods to ensure confirmation that the adjuvant is sterile.

5. For inactivated products, the methods describing the inactivation check test must be specified in detail in Section IV.

6. Confirmation of dating approval must be provided in Section VI.C.

B. Review of APHIS Form 2008

1. If an unsatisfactory sterility result is observed, the product is placed under Review Hold. The lifting of the Review Hold can be performed if the next two serials do not have unsatisfactory sterility results.

2. If two or more serials are produced in sequence with unsatisfactory sterility results, inform the firm's Reviewer in writing and notify an Inspection and Compliance Section Leader.

C. Serials submitted for consideration for marketing release not prepared in accordance with the Outline of Production/Special Outline (Process Deviation)

1. Review the applicable Outline of Production and/or Special Outline.

2. Review the Investigation Report from the licensee/permittee and determine if the risk assessment, CAPA, and conclusion are appropriate.

3. The investigation is required to evaluate the issue globally; if it does not address the issue globally, the report is insufficient. The Biologics Specialist is to follow up on if any other product (especially marketed product) has been affected or was involved.

4. If the licensee/permittee has conducted the applicable 9 CFR safety testing, **AND** the investigation appears appropriate, the Biologics Specialist can respond with **ICTEM0016**, *Process Deviation*, and allow the APHIS Form 2008 to be submitted for the product to be considered for marketing release.

5. The Product Code is placed on REVIEW HOLD as the exemption provision is suspended until the manufacturing process is under control.

   a. Notify the Reviewer by email of the action.

   b. The Specialist must notify the licensee/permittee in writing that future serials will not be considered eligible for consideration for marketing release unless tested in accordance with the applicable 9 CFR safety testing. The PEL Reviewer Manual, 4.5.1, instructions indicates: "The safety tests that the firm should perform if the exemption is suspended for any reason should remain in the Outline of Production." If the safety test requirement has been removed, the firm must add the requirement back to the Outline of Production.

   c. Future 2008 submissions will be required to list the testing of the applicable 9 CFR safety testing.

d. The licensee/permittee must successfully produce 10 consecutive serials in accordance to the Outline of Production for consideration of the reissuance of the exemption. The Review Hold Sticker on the back of the Review Hold sheet is used to track the number of serials.

D. Serials found during inspection or the CVB is notified that the product was not manufactured in accordance with the Outline of Production or the regulations AND released to the market.

1. Contact the Investigation Manager, an IC Section Leader, or IC Director. The licensee/permittee may initiate a Voluntary Stop Distribution and Sale action once the violation is discovered. If not: Provide a summary and the risk assessment and recommendation to the IC contact. Based on the risk assessment and Specialist's recommendation, minimally a Mandated Stop Distribution and Sale should be placed on the product **to all known persons to have received the product**. See VS Memo 800.57, Market Suspensions. See the latest version of **ICWI0033**, *APHIS Mandated Stop Distribution and Sale Procedures*.

a. The Mandated Stop Distribution and Sale letter (user level) should be initiated and sent to the licensee/permittee as soon as possible.

b. Regulatory actions:
   i. Obtain distribution list (quantities, dates, address)
   ii. Determine quantity not distributed
   iii. If the antigen lot is affected, determine if used in other products.

c. In order for the IC to lift the Mandated Stop Distribution and Sale, the serial(s) should undergo 9 CFR safety testing and the licensee/permittee performs a satisfactory root cause analysis investigation.

2. Determine if any other marketed product is affected as the Mandated Stop Distribution and Sale may be applicable to these products also.

3. The Product Code is placed on REVIEW HOLD as the exemption provision is suspended.

a. Notify the Reviewer by email of the action.

b. The Specialist must notify the licensee/permittee in writing that future serials will not be considered eligible for consideration for marketing release unless tested in accordance with the applicable 9 CFR safety testing. The PEL Reviewer Manual, 4.5.1, instructions indicates: "The safety tests that the firm should perform if the exemption is suspended for any reason should remain in the Outline of Production." If the safety test requirement has been removed, the firm must add the requirement back to the Outline of Production.

c. Future 2008 submissions will be required to list the testing of the applicable 9 CFR safety testing.

d. The licensee/permittee must successfully produce 10 consecutive serials in accordance to the Outline of Production for consideration of the reissuance of the exemption. The Review Hold Sticker on the back of the Review Hold sheet is used to track the number of serials.

4. The Notification letter or telephone calls from the licensee/permittee regarding the Mandated Stop Distribution and Sale letter to the user should be initiated immediately and must be reviewed by CVB-IC prior to distribution.

E. Inspection finding the Outline of Production or Special Outline is insufficient or not in compliance with 9 CFR 114.8(d).

1. See the current version of **ICWI0028**, *Exemptions to 9 CFR Part 109.1 and 109.2*.

2. Finding of an inaccurate or insufficient Outline of Production or Special Outline requires the Biologics Specialist to analyze the impact to the product prior to any regulatory action being taken.

3. Minimally, an action item needs to address the violation with the expectation the Outline of Production or Special Outline be updated to appropriately describe the preparation of the product.