

Inspection Techniques and Reporting Violations Related to 9 CFR 102.5(c)(1) and 114.8(d)

BACKGROUND

When auditing records or making observations during an on-site inspection, the Biologics Specialist (Specialist) utilizes the filed Outline of Production, Special Outlines, and regulations to determine compliance. It is critical that these foundational documents be accurate and sufficient in detail to allow a determination of compliance and consistency in preparation of quality product. It is also critical that the Outlines are adhered to in order to manufacture a consistent quality product.

The term Outline of Production will be the reference used for both Outlines of Production and Special Outlines for the remainder of the document.

REGULATIONS

1. 9 CFR 102.5(c)(1) “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.”

During the prelicensing phase of a product, critical and essential steps in the production and testing process should be documented; starting with the pivotal efficacy serial through the consistency serials. These steps must be included in the Outline of Production.

9 CFR 102.5(c)(1) also requires the product to be prepared according to the regulations. All products prepared must be according to the regulations unless specifically exempt in the Outline of Production.

2. 9 CFR 114.8(d) “Each licensee shall review each Outline of Production for accuracy and sufficiency not less frequently than once a year. Revisions necessary to bring an Outline of Production into compliance with the regulations shall be submitted to Animal and Plant Health Inspection Service.”

The review is expected to discover any inaccuracies or insufficiencies. An Outline of Production is inaccurate and insufficient if critical steps are not included.

DEFINITIONS

Critical Step: An important step, process, ingredient, piece of equipment, or a decision point, with respect to the final outcome.

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Examples of Critical Steps:

- Critical decision point – may be those that are of a Yes/No nature
 - Will the preparation of product proceed, or not proceed, if this operation is not performed?

- Critical step in a procedure, performed consistently in the preparation of the product and if deleted or altered, may affect the quality of the product or shelf life.

Outline of Production: [9 CFR 101.3(j)]: A detailed protocol of methods of manufacture to be followed in the preparation of a biological product. Title 9 CFR 114.8(a): The Outline of Production shall be prepared as prescribed in 114.9.

Detailed Outlines of Production are expected to list all critical steps in the preparation of the product. Outlines of Production are required to be reviewed for accuracy and sufficiency.

INSPECTION TECHNIQUES RELATED TO:

1. Possible Processes to Changes to the Outline of Production

As required in 9 CFR 102.5(c)(1), “No **changes** shall be made in preparation of a biological product without prior approval of the Administrator”.

In the majority of cases, data is required to be submitted for Center for Veterinary Biologics (CVB) review when a change to the Outline of Production is requested. Therefore, products ineligible for marketing release can be prepared outside of the parameters listed in the currently filed Outline of Production with the intent to submit the data as part of the request to make changes to the Outline of Production.

The preparation of the products outside the parameters listed in the currently filed Outline of Production cannot jeopardize or risk other processes, ingredients, or products.

Review serials prepared for these situations during inspection and ensure the following criteria was in place:

- a. The product contains CVB approved organisms/vectors/cells.
- b. The serial(s) are properly controlled (quarantined) until such time CVB-Policy, Evaluation, and Licensing (CVB-PEL) has approved the changes to the Outline of Production.
 - i. Samples may be requested as part of this review process and can be submitted.

 - ii. The APHIS Form 2008 marked as “Eligible for Release” for the product cannot be submitted prior to approval of the updated Outline of Production.

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If it has been, it should be a violation and may result in an Infraction Notification.

2. 9 CFR 102.5(c)(1)

- a. If there is evidence that the product was not prepared according to the Outline of Production, this is likely a violation of 9 CFR 102.5(c)(1).
- b. It is important to determine whether product was prepared outside the Outline of Production versus not documenting the preparation appropriately.
- c. Documentation must be available to substantiate that the preparation of product has been performed according to the Outline of Production currently on file with CVB. If documentation is not sufficient, this is likely a record keeping violation.

3. 9 CFR 114.8(d)

Documentation must be available to substantiate the Outline of Production has been reviewed for accuracy and sufficiency on a yearly basis. This means that each filed Outline of Production must be reviewed within the last 12 months by individuals who are familiar with the procedures currently used in the processes. The process and review must be adequately documented.

If the Outline of Production review is documented, but during the inspection there are findings regarding the lack of detail for critical steps or critical steps are not in the Outline of Production, it may be determined the review process is insufficient and the Outline of Production is inaccurate and insufficient.

Many establishments use manufacturing directions that usually contain more detail of the production process than does the Outline of Production. The Specialist needs to determine if there are critical steps being done and recorded that should be listed in the Outline of Production. If it is determined that the Outline of Production is missing critical details, the violation is usually of the minor to less serious nature unless the violation has been observed during previous inspections.

While the requirements in the manufacturing directives/standard operating procedures (SOPs) may be more precise, the requirements, ranges, parameters listed must be within the requirements, ranges, or parameters detailed in the Outline of Production.

Examples of Outlines of Production that are not accurate or sufficient:

- a. Manufacturing directives or SOPs that contain critical processes that are not listed in the Outline of Production.
- b. If the process described in the Outline of Production is ambiguous or is interpreted differently than intended.

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- c. If the PEL Reviewer has changed the Outline through Pen and Ink corrections, or requested changes on the APHIS Form 2015, and the Establishment has not incorporated those changes to the Outline at the yearly review or deadline stipulated by the Reviewer (see PEL Manual, Work Instruction 4.1 or current instruction).

VIOLATION AND INSPECTION REPORT CITATION

1. Title 9 CFR 102.5(c)(1)

If the establishment is not adhering to the Outline. The risk to the product must be evaluated by the inspector to determine categorization of the violation (see **ICSOP0105**, *Compliance Policy for Issuing Regulatory Actions*) and below.

If the establishment cannot substantiate that the Outline is being complied with. This is a violation of 9 CFR 116 if the inspector determines the step had a good probability of occurring. The risk to the product must be evaluated by the inspector to determine categorization of the violation (see **ICSOP0105**).

If an establishment is not preparing product according to the regulations, this is a violation of 102.5(c)(1). The risk to the product must be evaluated by the inspector to determine categorization of the violation (see **ICSOP0105**).

- i. Assess if the product was prepared to substantiate a change to the Outline of Production.
- ii. If an APHIS Form 2008 has been submitted to CVB for marketing release purposes and the product was not prepared according to the Outline of Production, this is a **serious** violation (see **ICSOP0105**).
- iii. **If the product has been released to the market**, the finding is usually a **serious** violation and if the establishment does not initiate a voluntary stop distribution and sale, contact the office to initiate a mandatory stop distribution and sale.

Violation – *Name, Code, Serial*, was not prepared in accordance with Outline of Production and (submitted APHIS Form 2008 for marketing release to CVB) or (the product was released to the market).

[Reference: 9 CFR 102.5(c)(1)]

Observation/Audit

Cite product and serial as well as any subsequent distribution actions.

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ACTION ITEM: (Liaison) agreed to prepare product intended for marketing release in accordance with the approved Outline of Production immediately.

2. Title 9 CFR 114.8 (d)

If the Outline is not sufficient or accurate based on audits, documentation, or observations made during the inspection. The risk to the product must be evaluated by the inspector to determine categorization of the violation (see **ICSOP0105**).

Violation – The Outline of Production for *Name, Code* was determined to be inaccurate and insufficient.

[Reference: 9 CFR 114.8(d)]

Observation/Audit

Cite product and the facts pertaining to the discovery of the violation.

ACTION ITEM: (Liaison) agreed that (name of establishment) will review the Outline of Production for accuracy and sufficiency. The inaccuracies and/or insufficiencies will be corrected within (timeline – dependent on the severity of the issue).