Animal and Plant Health Inspection Service

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Processes for Evaluating Compliance with Requirements of VS Memo 800.210 and VS Memo 800.57

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Source Document: Title 9 CFR 116.5(b), 105.1, 105.1(6)(b), VS Memo 800.57, 800.210

I. PURPOSE

To provide guidance to the IC Biologics Specialists in support of consistent review and expectations concerning evaluation of investigations concerning outline of production deviations, out of specification (OOS) deviations, or temperature excursions during inspections or submission to IC.

II. BACKGROUND

Title 9, *Code of Federal Regulations* (9 CFR), section 116.5 (b) requires: If, at any time, there are indications that raise questions regarding the purity, safety, potency, or efficacy of a product, or if it appears that there may be a problem regarding the preparation, testing, or distribution of a product, the licensee, permittee, or foreign manufacturer must immediately notify the APHIS concerning the circumstances and the action taken.

CVB published VS Memorandum 800.210 in 2010 allowing manufacturers the ability to investigate temperature excursions pre and post marketing release, and if no effect on the product through expiration was determined, the product may continue to be marketed without CVB notification.

In 2018, VS Memorandum 800.210 and 800.57 were revised to expand the regulatory flexibility and clarify the requirements concerning the investigation required to evaluate the quality of the effected product. Memorandum 800.57 concerns temperature excursions post marketing release and 800.210 concerns deviations prior to marketing release.

In 2021, CVB-IC initiated the new process for Issuance of Inspection Certificates. Inspection certificates will be issued for in-depth inspections of U.S. Veterinary Biologics Establishment Licensed sites. These certificates are issued to indicate the manufacturing site or sites have been inspected under U.S. laws and determined to comply with USDA's good manufacturing practices (GMP). To be aligned and comply with GMP practices, all licensed manufacturers that are issued Inspection Certificates must investigate all OOS events.

OOS deviations are usually events that result in testing No Test conclusions, failure of validity requirements, Unsatisfactory test results or a contamination event. The most common occurrence is during Outline of Production, Section V testing. OOS results includes *all* test or process results that fall outside the specifications or acceptance criteria established. The premise is that, under USDA GMP conditions of a controlled test or manufacturing process, as specified in the Outline of Production should result in a consistent quality product. Testing of the product, under USDA GMP conditions, should result in a valid Satisfactory conclusion (acceptable quality) if the test is conducted as per specifications. If a test or validity requirement of the test is not satisfactory, something

must be flawed to cause the OOS event and should be investigated. Any contamination event must also be investigated.
USDA regulations (9CFR 113.5(d)) requires that when the initial or any subsequent test is declared a No Test, the reasons shall be reported in the test records. The regulations in 9 CFR 113.5(d) are used, in part, as the basis to require the Licensee/Permittee to investigate the OOS event. A Licensee issued an Inspection Certificate is required to investigate any unexpected result or contamination event.

Examples:

- Licensee issued an Inspection Certificate: Required to investigate any OOS event.
- License/Permittee with no Inspection Certificate issued: Required under 113.5(d) to investigate a No Test OOS testing event but not Unsatisfactory testing event unless the investigation is required by the Specialist

III. SPECIALIST REVIEW OF INVESTIGATIONS DURING INSPECTION OR SUBMITTED INVESTIGATION DOCUMENTS

Section IV of VS Memorandum 800.210 contains the CVB expectations for the licensee and permittee investigations of the temperature excursion deviation effect or OOS impact to the quality of the product.

OVERVIEW: as per Section IV of VS Memo 800.210 – these should be minimum components of the investigation.

1. **Procedure in place at the firm (documentation) to address deviations/excursions/OOS event**
2. **Product risk analysis of deviation/excursion/ OOS**
3. **Root Cause investigation**
4. **Review of similar products/processes**
5. **Address other sites if applicable**
6. **Corrective and preventative action (CAPA) with review for effectiveness**

Procedure/Documentation to perform the investigation must include a systematic documented procedure to address temperature excursions /outline of production deviations/OOS events

1) The investigation should reference documentation that describes the investigation process. This process is usually found in an internal quality operating procedure.
2) Review the documented process used to obtain information and determine if the firm adhered to their internal process.
3) Failure to have documentation describing and recording the investigation process should result in regulatory action on any product evaluated and the loss of the licensees or permittees ability to self-evaluate temperature excursions and/or outline of production deviations until they can prove they have the quality control in place to appropriately perform the investigations.

Temperature Excursions

Temperature excursions may either be pre marketing release or post marketing release. This event is when a product, or an ingredient of the product is not held at the Outline of Production requirement, the regulations or specifications

The firm may define what they have scientifically determined as an acceptable temperature excursion.

If the acceptable temperate excursion includes parameters outside the Outline of Production temperature requirements, determine if scientific documented evidence is available to substantiate the limits allowed.

Example: Temperature data loggers outside the boxed or packaged product, or outside the shipping container, exceed temperature requirements for X degrees for X amount of time. The firm has data to substantiate that boxing or packaging configuration X will maintain product on the interior of the box or packaging within temperature requirements for X degrees and X amount of time.

Note: Other follow up questions can be addressed such as documentation of packaging configuration and temperature probes working appropriately.

Quality risk analysis. The risk analysis should minimally identify the risk to the quality of the product due to the temperature excursion **currently and at shelf life**.

1) The risk analysis must be supported by scientific data or evidence. Temperature excursions of limited duration and temperature magnitude that do not have supporting scientific data or evidence may be allowed to proceed if further real time evaluation is conducted. This evaluation should minimally be utilizing potency testing at mid dating, and one month pre expiration, and escalated adverse event monitoring.
2) Failure to address the **current effect** on quality or the lack of evaluation is considered a major defect in the investigation, and may result in a Hold Release or APHIS Mandated Stop Distribution and Sale initiated after consulting with CVB-IC Management.
3) **A major defect** in the investigation should result in loss of the Licensee or Permittee (all sites) the ability to utilize VS Memo 210 or 800.57 (self-evaluate the outcome of deviations or temperature excursions) until the firm can prove they have the quality system in place to appropriately perform the investigations.
4) The risk analysis must include the evaluation of **the effect on the shelf life** of the product.
    a. Many firms may not have data to evaluate the effect on shelf life. If the data is not available and the firm elects to monitor or evaluate real time effect on the product, this may be an acceptable alternative if reasonable. This is usually accomplished through potency testing at frequent intervals.
    b. Failure to address how the shelf life may be affected or lack of evaluation would be considered a major defect in the investigation.
    c. The failure should result in loss of the Licensee or Permittee (all sites) the ability to self-evaluate the outcome of temperature excursions and outline of

production deviations until they can prove they have the quality steps in place to appropriately perform the investigations.

i) The firm can elect to initiate potency testing of a sample that has been subject to similar conditions and/or notify customers to proactively report adverse events.

ii) Failure to take corrective action should result in regulatory action such a Hold Release or APHIS Mandated Stop Distribution and Sale. Consult with CVB-IC Management if this occurs.

Root Cause Analysis

1) This part of the investigation is an indicator of the firm's commitment to enhance their quality performance.

2) Identification of the general problem - the problem statement, excursion or deviation should be as clear and concise as possible.
Note: This is NOT THE ROOT CAUSE. The identification of the problem is the event or issue.Any indication by the firm that the issue or cause is the root cause indicates they are not prepared to perform a quality investigation.

3) Information gathering on issue should include:
- **a.** Information regarding event.
- **b.** Has issue happened before?
- **c.** Has there been similar incidences?

4) Drafting causal factors – tools such as fishbone, affinity diagram, Effect Analysis, 5 whys, etc., are used.

5) Define the **root cause** or probable root cause based on the data and analysis. Some excursions or deviations may not have a definitive root cause. A firm may list several possible root causes and provide CAPAs for each. Once the root cause has been determined, there are four primary actions that may be taken.
- **a. Adaptive** - Action that allows the adaptation or ability to live with the problem situation and still operate within daily objectives. The issue had no quality effect or regulatory requirement. This is usually seen with internal SOP or Directives deviations.
- **b. Interim/Correction** - Action that alleviates the immediate effects of the problem and buys time before a corrective action is implemented.
- **c. Corrective** - Action that eliminates the problem permanently so that it does not occur again at the site or other sites.
- **d. Preventative** - Action that anticipates potential problems and eliminates the most likely causes of the problem so they are less likely to occur in all areas of operation.

Similar occurrences or processes or possibility of similar occurrence

The investigation should address the possibility of commonalities with other products or processes that may have a similar occurrence or likely to have a similar occurrence. This should entail all sites on the establishment license.

Address other site implications
The investigations should address how the firm communicated the incident and investigation with other sites on the establishment license.

Corrective and Preventative Action (CAPA) with effectiveness review

1) The degree of corrective and preventive action taken to eliminate or minimize actual or potential issue must be appropriate to the magnitude of the problem and proportionate with the risks identified.
2) There are four primary actions that may be taken.
   a. **Adaptive -** Action that allows the adaptation or ability to live with the problem situation and still operate within daily objectives. The issue had no quality effect or regulatory requirement. This is usually seen with internal SOP or Directives deviations.
   b. **Interim/Correction -** Action that alleviates the immediate effects of the problem and buys time before a corrective action is implemented.
   c. **Corrective -** Action that eliminates the problem permanently.
   d. **Preventative -** Action that anticipates potential problems and eliminates the most likely causes of the problem so they are less likely to occur in all areas of operation.
3) A plan to monitor the effectiveness and evaluate effectiveness should be included.
   a. The plan must include timelines and deadlines.
   b. If inspecting site: The completed investigation should include the evaluation.

Outline of Production Deviations
Outline of production deviations are allowed to be assessed by the licensee/permitee under VS Memorandum 800.210 only pre - marketing CVB release. Deviations found post marketing release are subject to regulatory action. See CVB-WI-5272.

The process of evaluating deviations to the outline of product is similar to the post release temperature excursion expectations.

A **systematic documented procedure** to address temperature excursions and/or outline of production deviations must be in place at the licensee or permittee.

1) **Quality risk analysis**. The risk analysis should identify the risk to the quality of the product due to the deviation **currently and at end of shelf life**.
   a. The **investigation risk analysis** must be completed prior to requesting marketing release of the product line or serials.
      Note: The investigation may not be completed as ongoing potency, adverse events, and CAPA evaluation may be in place and ongoing.
   b. The risk analysis must be supported by scientific data or evidence.
   c. All evaluations should minimally use potency testing and escalated adverse event monitoring. This may be on-going and part of the investigation.
   d. If the deviation occurs where the in process batch may be used in multiple serials, all the serials should be monitored and tested.
   e. Failure to address the **current effect** on quality or the lack of evaluation would be considered a **major defect** in the investigation.

   i. A Hold Release or Mandated Stop Distribution and Sale may be initiated after consulting with CVB-IC Management.
   ii. The failure should result in loss of the Licensee or Permittee (all sites) to self-evaluate the outcome of deviations or temperature excursions until they can prove they have the quality control in place to appropriately perform the investigations.

f. Temperature excursions of limited duration and temperature magnitude that do not have supporting scientific data or evidence may be allowed to proceed if further real time evaluation is conducted. This evaluation should minimally utilize potency testing and escalated adverse event monitoring.

g. The risk analysis must include the evaluation of **the effect on the shelf life** of the product.
   i. Many firms may not have data to evaluate the effect on shelf life. If the data is not available and the firm elects to monitor or evaluate real time effect on the product, this may be an acceptable alternative. This is usually accomplished through potency testing at frequent intervals.
   ii. Failure to address how the shelf life may be affected or lack of evaluation would be considered a major defect in the investigation.

2) **The investigation parts: Root Cause Analysis, Similar occurrences or processes or possibility of similar occurrence, Address other site implications, Corrective and Preventative Action with effectiveness review are treated similarly to temperature deviations.**

Out of Specification – OOS – Deviation Events

OOS events should follow the same investigation process by the Licensee/Permittee as required in VS Memorandum 800.210.

1) The OOS investigation should be thorough, timely, unbiased, well-documented, and scientifically sound.
2) The purpose of the investigation is to determine the cause of the OOS result.
3) Corrective and Preventative Action (CAPA) with effectiveness review are important to address the issue.
4) The source of the OOS result should be identified either as an aberration of the measurement process or an aberration of the manufacturing process.
5) Even if a batch/serial is rejected based on an OOS result, the investigation is necessary to determine if the result is associated with other batches/serials of the same product or other products.
6) Batch/serial rejection does not negate the need to perform the investigation.
7) Failure of the Licensee/Permittee to perform an investigation when a NT is found during testing is a violation of 9 CFR 113.5(d).
8) Failure of the Licensee, that has been issued an Inspection Certificate, to perform an OOS event investigation appropriately requires a Letter of Advice, under 9 CFR 114.1, subsequent violations could result in further regulatory action.