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BIOSPECTRA

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PROCESS CLEANING VALIDATION MASTER PLAN

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1. INTRODUCTION

The cleaning process developed by BioSpectra must conform to the FDA's "Guide to Inspections Validation of Cleaning Processes" (Inspection Guides, Validation of Cleaning Processes (7/93), 2010) DCN:20-003647 and "APIC Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants." DCN:20-003596. In addition to ensuring that the FDA guidelines are met, for each BioSpectra process that requires a cleaning process, BioSpectra will develop a set of procedures that must be followed. In these procedures the cleaning process, sampling methods, analytical testing methods and acceptance criteria will be defined.

The validation protocol will include the specific cleaning process, the exact sampling locations and sampling methods, the length of time of the cleaning process, if applicable, any critical parameters (for example, water source and purity, time, temperature, pressure, cleaning agents), acceptance criteria to be documented and observed, as well as analytical tests.

The validation report will include all of the supporting documentation from the activities performed for the validation protocol. This will include a conclusive statement of whether the cleaning process has been validated and under what conditions it is considered a validated process. This will also include a statement of waiting periods, both before and after cleaning.

All steps in the cleaning process validation will be documented. The documentation involved in the validation process allows BioSpectra to demonstrate that the cleaning process is working as it is intended to and that it has been tested and proven effective.

2. RESPONSIBILITIES

A validation team must be defined at the start of each validation study. This team should consist of a representative member of the following departments including but not limited to: appropriate member(s) of the Quality Unit, Manufacturing, and Management. If personnel from other departments prove to be a resource to the validation process, then they should additionally be included in the validation team.

The validation team is responsible for determining the parameters of the validation. This should include: the validation methodology, the analytical methods used, the critical parameters that need to be monitored, the acceptance criteria and the terms of revalidation. Once the validation parameters have been established, it is the responsibility of the validation team to write the validation/revalidation protocol.

It is the responsibility of the Executive Director of Manufacturing, or qualified designee to ensure that the cleaning procedures for validation are accurate and feasible for production personnel to execute. It is also the responsibility of the Executive Director of Manufacturing to ensure that the production personnel carrying out the validation protocol are qualified to be completing the tasks. Additionally, it is the responsibility of the Executive Director of Manufacturing, or qualified designee to ensure that any new equipment utilized in an existing process is included as a revision to the product specific batch record with the appropriate rinse volumes required for cleaning the equipment in accordance with the approved change control. This may include monitoring of any new tasks or procedures. This will help to ensure that the validation protocol and any subsequent standard operating procedures (SOPs) are as detailed as necessary to complete the cleaning tasks in the same way each time they are performed. It is the responsibility of the Executive Director of Manufacturing or qualified designee to write any procedures that are needed for or because of the validation in regard to the actual cleaning procedures that will be followed by the production personnel.

It is the responsibility of the Qualification Lead, or qualified designee to ensure that the equipment to be used for the protocol is completely qualified and ready to use in accordance with the Equipment Qualification Master Plan. It is the responsibility of the Executive Director of Manufacturing, or qualified personnel who are delegated the task, to provide the surface area of the equipment. It is the responsibility of the Executive Director of Manufacturing to assist the authors of the validation protocol and cleaning and sampling procedures in identifying locations for equipment potentially difficult to be cleaned effectively. It is also the responsibility of the Executive Director of Manufacturing to identify what equipment must be disassembled to effectively clean the equipment. A preventative maintenance program will already be in place prior to the start of the cleaning validation protocol. This will be completed by the Equipment Preventative Maintenance Supervisor and Qualification Lead. It is the responsibility of the Manufacturing Technical Writer or qualified personnel to write any procedures regarding the assembly, disassembly, and operation of equipment required for the Cleaning Validation.

It is the responsibility of the QC Manager with support from the Associate Director, Compliance, as needed, to determine the analytical methodology that will be used to ensure that the equipment is clean. The analytical method to be used must be a validated method. The analytical method validation must follow the guidelines outlined in the Analytical Methods Validation Master Plan. It is the responsibility of the Quality Unit to determine the acceptance criteria and residue limits required. The QC manager must ensure that the limit of detection and limit of quantitation set for the

chosen analytical method prove that the analytical method is capable of accurately detecting the residue limit. Sampling locations and quantity of samples required will be determined by the validation team based on the most representative locations within each piece of equipment. It is the responsibility of the QC Manager or qualified personnel to review data collected from analysis that is obtained from the validation. It is the responsibility of the QC Manager or qualified personnel to develop any procedures regarding the analytical methods developed for or because of the validation.

It is the responsibility of the validation team to ensure that the guidelines in this Process Cleaning Validation Master Plan are reflected in each individual cleaning validation protocol. The Associate Director, Compliance or qualified personnel will be the lead of each validation team and will schedule all validation meetings. It is the responsibility of the Associate Director, Compliance to ensure that the validation follows cGMP guidelines. The QC Manager, Associate Director, Compliance, and Executive Director of Manufacturing will ensure the validation is completed in a timely fashion with all documentation correct and complete. It is the responsibility of the Associate Director, Compliance to ensure that the protocol is approved by all appropriate parties prior to the start of validation. The Associate Director, Compliance is responsible for all documentation related to the validation. The validation team is responsible for any change control requirements that arise due to the validation. It is also the responsibility of the Associate Director, Compliance to ensure that all necessary protocols and documentation are completed by the end of the validation. This will ensure that the validated procedures are followed the same way each time the cleaning process is required.

3. DEFINITIONS

- *Validation Team:* The Validation Team will consist of at least one member from each of the following departments: Quality Unit, Manufacturing, and Management. There may be instances where other departments are needed and personnel will be assigned from those departments as needed.
- *NOEL:* No Observed Effect Level (Hall)
- *ADI*: Acceptable Daily Intake
- *MACO*: Maximum Allowable Carry Over
- *EPA:* Environmental Protection Agency
- *Adulteration Limit:* The limit calculated based on a 10 ppm carry over from product to product
- *Toxicological Limit:* The limit calculated based on the LD_{50} of the products being cleaned for
- *LOD:* Limit of Detection
- *LOQ:* Limit of Quantification
- *Percent Recovery:* Percentage of material able to be recovered during analysis

- *Clean Hold Time (CHT):* The length of time equipment may remain idle and still be considered clean
- *Dirty Hold Time (DHT):* The length of time the equipment may remain dirty and still be able to be cleaned utilizing the standard validated cleaning method
- *Routine Cleaning / Periodic:* Cleaning performed using water only during or at the end of a batch
- *End of Campaign Cleaning:* Cleaning performed using detergent (i.e.: CIP 100/150/200, etc.) at the completion of a campaign or prior to product change-over
- *After Maintenance Cleaning*: A routine cleaning performed after maintenance personnel have completed a preventative maintenance (PM) or work order (WO) unless specified differently due to the work performed
- *Visually Clean*: The absence of visible residue on a surface
- *Recovery Factor (RF):* The percent recovery obtained during recovery studies for a qualified individual who performs the swabs and rinses, as applicable
- *Swab Solvent Volume (SSV):* The volume of solvent used in the applicable vial where the swab is placed for analysis of residues
- *Swab Area (SA):* The surface area of the swabbing area in in^2 based on completed recovery studies
- *Rinse Volume (RV):* The Final Rinse Volume using Water for Injection (WFI) or Purified Water in Liters as detailed in the Cleaning Reference Sheet
- *Rinse Area (RA):* The sum of the rinse area for the equipment derived from the individual surface areas listed in the respective Cleaning Reference Sheet
- *Shared Surface Area (SSA)/Total Surface Area:* The sum of the shared surface area of the equipment derived from the individual surface areas listed in the respective Cleaning Reference Sheet

4. REFERENCES

- BioSpectra Procedures:
  - Analytical Methods Validation Master Plan
  - Annual Product Reviews
  - Cleaning Validation FMEA Template
  - Cleaning Worksheet Procedure
  - Discrepancy Investigation Procedure
  - Equipment Qualification Master Plan
  - QC Laboratory Investigation Procedure
- External References:
  - *Inspection Guides, Validation of Cleaning Processes (7/93).* (2010, June 14).
  - *APIC Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants*

5. ACCEPTANCE CRITERIA DETERMINATION

Acceptance criteria will need to be determined prior to the start of the validation studies. The acceptance criteria must be calculated in at least two different ways: Adulteration Limit and Toxicology Limit, and should be calculated to show the MACO Limits, Individual Swab Limit

Calculations, and Individual Rinse Limit Calculations. The calculation that yields the lowest specification for both product and detergent should be utilized to establish the respective acceptance limits unless otherwise scientifically justified by the Validation Team. During Cleaning Validation Protocol execution, the cleaning limits reference the worst-case minimum batch size listed in the process room specific cleaning reference sheet.

1
General Limit Product

Product Adulteration Limit (AL) Calculation:

$$AL\ MACO\ (mg) = 10\ ppm\ (\frac{mg}{kg})\ x\ (Worst\ Case\ Minimum\ Batch\ Size\ (kg)$$

2
General Limit Detergent

Detergent Toxicology Limit (TL) Calculation:

$$TL\ MACO\ (mg) = \frac{(LD_{50}\ (\frac{mg}{kg}))\ x\ (Worst\ Case\ Minimum\ Batch\ Size\ (kg)}{1000\ (Safety\ Factor))}$$

3
Individual Swab Limit Product

Product Adulteration Limit (AL) Calculation:

$$AL\ (ppm) = \frac{(10\ ppm\ (\frac{mg}{kg}))\ x\ (Minimum\ Batch\ Size(kg)\ x\ (Swab\ Area\ (in^2) x\ Recovery\ Factor\ (\%))}{(Shared\ Surface\ Area\ (in^2)\ x\ Swab\ Solvent\ Volume\ (L))}$$

4
Individual Swab Limit Detergent

Detergent Toxicology Limit (TL) Calculation:

$$TL\ (ppm) = \frac{(LD_{50}\ (\frac{mg}{kg}))\ x\ (Minimum\ Batch\ Size\ (kg)\ x\ (Swab\ Area\ (in^2))\ x\ Recovery\ Factor\ (\%))}{(Shared\ Surface\ Area\ (in^2)\ x\ Swab\ Solvent\ Volume\ (L))}$$

5
Individual Rinse Limit Product

Product Adulteration Limit Calculation:

$$AL(ppm) = \frac{(10\ ppm\ (\frac{mg}{kg}))\ x\ (Minimum\ Batch\ Size(kg)x\ (Rinse\ Area\ (in^2))}{(Shared\ Surface\ Area\ (in^2)\ x\ Rinse\ Volume\ (L))}$$

6
Individual Rinse Limit Detergent

Detergent Toxicology Limit Calculation:

$$TL\ (ppm) = \frac{(LD_{50}\ (\frac{mg}{kg}))\ x\ (Minimum\ Batch\ Size\ (kg)x(Equipment\ Surface\ Area(in^2))}{(Shared\ Surface\ Area\ (in^2)\ x\ Rinse\ Volume\ (L))}$$

The FDA requires that "The firm should challenge the analytical method in combination with sampling methods used to show that contaminants can be recovered from the equipment surface and at what level" (Nassani, 2006).

Utilizing all the information provided, the validation team must write the initial cleaning validation protocol for the intended process/equipment. This protocol must be reviewed and approved by all members of the validation team.

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6. PROCESS CLEANING VALIDATION PROTOCOL

The process cleaning validation protocol will include the following at a minimum: purpose, scope, responsibilities, references, sampling method determination procedure, protocol execution, and reporting.

Purpose: An introduction containing a brief description of the purpose and procedure of the validation protocol will be written.

Scope: The scope should define the process to be evaluated and the limitations of the work (Tunner). The scope should define at what location the procedure will be carried out and who in the firm the procedure will effect.

Responsibilities: Defines the actions to be taken by the validation team members.

References: Will include current manufacturing process description, analytical method determination procedure, cleaning method determination procedure, and manufacturing cleaning procedure.

Sampling Method Determination Procedure: This section will detail what sampling is required and how to perform swab sampling correctly.

Protocol Execution: Outlines the procedure for the execution of the cleaning validation during product changeover or at the end of a campaign, cleaning activities, and cleaning verification between batches within a campaign. Rinse samples will be collected during batches of a campaign, while executing cleaning validation studies. These rinses will be monitored for product residues and microbial residues, where applicable, and will be used for limit development, as applicable. Coverage testing requirements, where applicable, will be detailed in the specific Cleaning Validation Protocol or Spray Coverage Qualification Protocol prior to Cleaning Validation execution. If Coverage Testing is unable to be completed, then the manufacturer of the equipment and Spray Ball will be referenced, as it pertains to coverage details and space/square footage of equipment.

Reporting: Provides guidelines for issuance of the summary report.

7. PROCESS CLEANING VALIDATION REPORT

The process cleaning validation report should be written after the protocol has been executed and all data has been analyzed. “A final validation report is expected by the FDA” (Tunner). It is the responsibility of the Associate Director, Compliance or qualified personnel, as detailed in the respective Cleaning Validation Protocol, to write the report with support from the validation team and the data obtained during the validation.

The report should include a brief introduction of the scope of the validation, the time frame in which it occurred, the cleaning procedure followed, methods used for analysis, and the lots of material that were manufactured before the cleaning validation protocol was executed.

The Report must consist of an analysis of all data obtained during the validation. Data obtained should be analyzed to ensure that the cleaning process is consistently meeting specifications. If the process cannot consistently meet specifications, then the cleaning process should be considered inadequate and re-evaluated. This re-evaluation will be considered the annual review.

Any Discrepancy Investigations that occurred during the validation must be documented according to BioSpectra's Discrepancy Investigation Procedure. The discrepancies must detail any additional full validation runs that are required in order to validate that the corrective action was sufficient (Tunner). Any Laboratory Investigations that occurred during the validation must be documented according to BioSpectra's QC Labroatory Investigation Procedure.

Finally, the report should contain a conclusion. The conclusion should be an overview of the validation that was completed and under what circumstances the cleaning process is to be considered validated. There must be a clear statement regarding the validation status of the cleaning process. There must also be a clear statement of when the cleaning process is due for revalidation, as discussed in Section 8.

8. REVALIDATION

Each cleaning process must have a documented review on an annual basis per Annual Product Reviews DCN:16-000343. This review will allow the reviewers to determine whether revalidation is necessary. This review should include a review of any pertinent change controls and any related Laboratory Investigations or Discrepancy Investigations. This review should also include any "cleaning failures or issues raised with the procedure and any minor changes to the procedure itself, the cleaning facility, the equipment cleaned, or the soils encountered" (Tunner). Any major changes to the cleaning process will require revalidation of the process. This review must be completed regardless of whether a revalidation is required (Tunner). This review is only required after a validation has been completed. It is not required to be created annually, while still in the validation process.

9. ROUTINE CLEANING

For all products manufactured at BioSpectra facilities, a routine cleaning will be conducted every ten batches (batch lot numbers are consecutive, if the lot number ends in "0" Manufacturing performs a routine cleaning after the batch is manufactured) or at the end of a campaign for dedicated process equipment. Routine cleaning can also be performed prior to ten batches on non-product dedicated process equipment based on pre-validation studies and validation protocols. Routine cleaning limits are established in the cleaning validation protocol. Routine cleaning will be conducted with WFI or USP Purified Water only. No detergents will be used unless otherwise justified in the cleaning verification portion of the cleaning validation protocol. If after ten batches, all acceptance criteria are met during the routine cleaning, then the campaign count will be reset to one. If routine cleaning fails to meet established acceptance criteria, then the equipment in question must be cleaned utilizing detergent in order to reset the campaign count to one. The campaign count should not exceed ten batches before routine cleaning has been executed.

10. HOLD TIMES

The period and when appropriate, conditions of storage of equipment before cleaning, commonly referred to as dirty hold time (DHT) and the time between cleaning and equipment reuse, prior to additional cleaning, commonly referred to as clean hold time (CHT), should form part of the validation of cleaning procedures. This is to provide confidence that routine cleaning and storage of equipment does not allow potential for buildup of degradation products that may not be removed by the standard cleaning procedure and does not allow for the possibility of microbial contamination of equipment, and to ensure that these possible risks are properly assessed and controlled. These times will be determined based on process risk assessments and/or at the completion of the cleaning validation study. The timeframe of 10 days for Clean Hold Time studies and 48 hours to visually clean for Dirty Hold Time is required at minimum.