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Sodium Hydroxide 1N Solution Bio Excipient Grade Process Room M03 2021 Validation Report

Validation Protocol for the Manufacture of:

Sodium Hydroxide 1N Solution

To be Manufactured as the Following Codes:

Bio Excipient Grade and Below Compliance Grade

To be Manufactured at:

BioSpectra, Inc., 100 Majestic Way
Bangor, PA 18013

In Compliance with the Standards of:

The Joint IPEC – PQG Good Manufacturing Practices
ICH Q7 Good Manufacturing Practice Guidance

Manufactured to be Suitable for Use as:

An Excipient

TABLE OF CONTENTS

1. INTRODUCTION:

This validation report summarizes the execution of the Sodium Hydroxide 1N Solution Validation Protocol, DCN: BSI-PRL-0385 v.1.0 (historical DCN: 21-003036). One batch was manufactured in Process Room M03 at the BioSpectra, Bangor, PA facility. This validation confirmed that the Sodium Hydroxide 1N Solution Bio Excipient Grade manufacturing process is in a state of validation when the current batch record, Sodium Hydroxide 1N Bio Excipient Grade Batch Record, DCN: BSI-MPR-0041 (historical DCN: 21-001783), is followed for manufacturing.

In the *2011 Process Validation: General Principles and Practices Guidance*, the FDA defines validation, specifically process validation as: "The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product."

This validation was a concurrent validation, as it ensured that the process conforms to the pre-established validation parameters. A concurrent validation requires that all finished goods analysis be completed and approved before each validation lot is approved for commercial distribution. The Critical Process Parameters (CPP) for the manufacturing process were monitored and documented during the validation. The CPP's were defined prior to executing the validation protocol using tools such as process mapping and Failure Modes Effect Analysis (FMEA) and Cause & Effect matrix. The data collected during the execution of the protocol was analyzed to determine whether the process controls were adequate in assuring that the material conformed to the specifications described in the protocol and the current revision of the batch record.

2. OBJECTIVE:

The objective of this report is to summarize the data gathered during the validation protocol execution and provide a conclusion on the state of the validation for the Bio Excipient Grade manufacturing process of Sodium Hydroxide 1N Solution manufactured in Process Room M03.

3. SCOPE:

This report applies to:

- The execution of the Sodium Hydroxide 1N Solution Validation Protocol, DCN: BSI-PRL-0385 v.1.0 (historical DCN: 21-003036), which was executed in Process Room M03 located at the BioSpectra Bangor, PA facility.
- The manufacturing process for Sodium Hydroxide 1N Solution Bio Excipient Grade as described in the current Sodium Hydroxide 1N Bio Excipient Grade Batch Record, DCN: BSI-MPR-0041 (historical DCN: 21-001783).

- All Manufacturing and Quality personnel involved in the creation, execution and documentation of the protocol and report.

The validation protocol validated the manufacturing process of Sodium Hydroxide 1N Solution Bio Excipient Grade in Process Room M03 at the BioSpectra Bangor, PA facility. Specifications and approval requirements for all raw materials (RM) and components have been created; therefore, the RM and components are not covered by this report except that only approved RM and components were used. This report, training records, testing and the executed protocol are filed in the Sodium Hydroxide 1N Solution Bio Excipient Grade validation binder. The batch records for the validation batch, executed protocol and uniformity testing are attached electronically in MasterControl to this report.

The validation was intended to represent the grade of Sodium Hydroxide 1N Solution manufactured at BioSpectra's Bangor, PA facility sold as Bio Excipient Grade. The Bio Excipient Grade represents assurance of suitability for end use as an Excipient, manufactured in accordance with the guidelines of ICH Q7 Good Manufacturing Practice Guide. The following Sodium Hydroxide 1N solution product quality codes will be validated within the scope of this validation:

- Bio Excipient Grade: NAHY-3153
- Bio Pharma Grade: NAHY-4153

4. CHANGES SINCE LAST REVISION:

This is the first validation study for Sodium Hydroxide 1N Solution Bio Excipient Grade in Process Room M03.

5. EXECUTED SUMMARY:

The validation protocol contained executable forms which documented the manufacturing, sampling and analytical testing of the validation batch. Each of the forms were completed during the execution of the protocol. The forms were reviewed by Quality to ensure that the validation protocol was executed as written.

6. REFERENCES:

6.1. Reference Documents

6.1.1. BSI-ATM-0047, Sodium Hydroxide 1N Testing Methods

6.1.2. BSI-DGM-0102, Process Room M03 Processing Area FMEA

6.1.3. BSI-DGM-0241, Sodium Hydroxide 1N Process Mapping

6.1.4. BSI-DGM-0242, Sodium Hydroxide 1N Process Flow Diagram

6.1.5. BSI-DGM-0243, Sodium Hydroxide 1N FMEA and C&E Matrix

6.1.6. BSI-MPR-0041, Sodium Hydroxide 1N Bio Excipient Grade Batch Record

6.1.7. BSI-PRL-0385, Sodium Hydroxide 1N Solution Validation Protocol

6.1.8. BSI-RPT-0412, Process Room M03 Process Installation Qualification Report

6.1.9. BSI-RPT-0415, Process Room M03 Process Area Operational Qualification Report

6.1.10. BSI-RPT-0416, Process Room M03 Process Area IQ/OQ Addendum Report

6.1.11. BSI-RPT-0447, Degradation and Impurity Report: Sodium Hydroxide

6.1.12. BSI-RPT-0743, Process Room M03 Tube Welder IQ/OQ/PQ Report

6.1.13. BSI-SOP-0010, Documentation Entry and Error Correction

6.1.14. BSI-SOP-0093, QC Laboratory Investigation Procedure

6.1.15. BSI-SOP-0136, Stability Testing Program

6.1.16. BSI-SOP-0137, Discrepancy Investigation Procedure

6.1.17. BSI-SOP-0292, Manufacturing Process Validation Master Plan

6.1.18. BSI-SOP-0435, Equipment Qualification Master Plan

6.1.19. BSI-SPC-0266, NAHY-3153 Sodium Hydroxide 1N Bio Excipient Specifications

6.2. Reference Codes and Standards

6.2.1. ANSI American National Standards Institute

6.2.2. ASTM American Society for Testing and Materials

6.2.3. ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

6.2.4. NIST National Institute for Standards and Technology

6.2.5. The IPEC-PQG Joint Good Manufacturing Practice Guide

6.2.6. UL Underwriter's Laboratory

7. RESPONSIBILITIES:

TABLE 1: RESPONSIBILITIES

Group / Individual	Responsibilities
Validation Team	Review and approve the protocol and report.
	Review and approve protocol changes in writing including deviations and discrepancies.
	Ensure proper training is conducted to complete the requirements of this protocol for their applicable section.
Manufacturing	Manufacturing Operators or designee performing sampling in accordance with this procedure will be responsible for the collection of the samples and deliveryof the samples to the QC Laboratory.
	Manufacturing Supervisors or designee are responsible for ensuring that manufacturing operators are appropriately trained before executing any steps in this validation protocol.
Process Technology, or designee	Create Support Documents associated with this validation study and file them in MasterControl.
	Authors and edits the Validation Protocol and associated reports.
	Verifies Qualifications and Calibrations are complete and current for all equipment and measuring tools associated with this validation.
	Conducts or ensures training is conducted for the Validation protocol procedures and expectations. Training will be documented using the appropriate training verification forms and the completed Training Verification Form(s) will be provided to the Human Development Department.
	Summarizes and attaches all applicable data to the Validation BinderValidation Report located on MasterControl.
	Writes the Validation Report and submits for review and approval to the validation team.
Laboratory Services	Department Representative on the Validation Team will ensure Analyst performing analysis associated with this protocol is trained on the analysis and the expectations of this Validation Study
	Completes testing in accordance with the analysis listed in this protocol.
	Submits test results and summary sheets to Process Technology for creation of the Validation Report.
Quality Assurance	Department Representative on the Validation Team will ensure the documentation is compliant with BioSpectra's Validation Master Plan and Good Manufacturing Practices.
	Verifies that the Batch Record, FMEA, C&E Matrix, Process Map, Process Flow Diagram comply with the expectations of the Validation Protocol.
	Completes all Quality Review and Approval Required in the Validation Protocol documents.

8. PROCESS DESCRIPTION

The detailed process description can be found in Section 8 of the Sodium Hydroxide 1N Solution Validation Protocol, DCN: BSI-PRL-0385 v.1.0 (historical DCN: 21-003036).

9. SUMMARY:

The manufacturing of the validation batch occurred on 2/8/21 to 2/10/21. During the manufacturing of the validation batch, the CPP values prescribed in the validation protocol were met. The validation batch met specifications for the required analyses, including finished goods and uniformity testing. Additionally, in-process samples were taken to ensure normality was met before finished goods packaging. During or as a result of the manufacturing of the validation batch, there was three discrepancy investigations issued, BDI21-43, BDI21-44 and BDI24-78.

Protocol execution assured that the manufacturing process for Sodium Hydroxide 1N Solution Bio Excipient Grade, consistently produces material that meets a set of pre-determined specifications and quality attributes. The validation confirmed that the Sodium Hydroxide 1N Solution Bio Excipient Grade manufacturing process is in a state of validation. One batch of Sodium Hydroxide 1N Solution was manufactured according to the current revision of the batch record. In-process analysis and the final quality control analysis results were used to determine the process is capable of producing material of acceptable quality.

10. MANUFACTURING OBSERVATIONS:

All instruments used during the manufacture of the validation were calibrated, the instruments and calibration dates are listed in the following table. The instruments listed are in the batch record, the calibration information is summarized from calibration records.

Manufacturing of:

- **NH3153-001-0221-PV was manufactured on 2/8/21 to 2/10/21**

TABLE 2: MANUFACTURING INSTRUMENTATION CALIBRATION VERIFICATION

Description	Serial Number/ID	Calibration Date	Due Date
Scale	ZFS09	1/12/21	5/31/21

The critical process parameters are documented below in Table 3: Critical Process Parameters (CPP).

TABLE 3: CRITICAL PROCESS PARAMETERS (CPP)

Process Step	Parameter	Justification
Raw Material Charge	Approved Sodium Hydroxide 10N Solution	All Sodium Hydroxide utilized for this manufacturing must be approved material. Quantity will be determined based on calculation referenced in process description using expected batch yield and concentration.
	Water for Injection	WFI must be obtained from BioSpectra's qualified water system. Quantity will be determined based on calculation referenced in process description using expected batch yield and concentration.
Agitation	Agitation	Agitation will be performed according to the following conditions: 20 to 35 Hz for a minimum of 120 minutes prior to sample 1 and a minimum of 30 minutes prior to sample 2.
Final Normality Adjustment (if required)	Calculate Adjustment Volume of WFI or NaOH 10N	Calculated final adjustment volume of WFI or NaOH 10N to achieve desired concentration.
	Agitation	Agitation will be performed according to the following conditions: 20 to 35 Hz for a minimum of 120 minutes prior to sample 1 and a minimum of 30 minutes prior to sample 2.
	0.95-1.05N	Confirmation of final product homogeneity verification based on two consecutive passing results.
Sterile Fill/Packaging	Sterile Filtration	Sterile filtered through a 0.2 Micron STyLUX® ST0.2 UltraCap ® H.D. Filter.
	Packaging	Packaging and testing of the finished product.

TABLE 4: BATCH 1 PRODUCTION SUMMARY

		Batch 1 Lot Number:	NH3153-001-0221-PV
CPP		**Specification**	**Validation Result**
Raw Material Charge	Approved Sodium Hydroxide 10N Solution	All Sodium Hydroxide utilized for this manufacturing must be approved material. Quantity will be determined based on calculation referenced in process description using expected batch yield and concentration.	NaOH 10N Calculated Qty – 1022 kg NaOH 10N lot used: NH4100-071-1020 – 396.5 kg NH4100-049-0720 – 234.5 kg NH4100-079-1120 – 391.0 kg
	Water for Injection	WFI must be obtained from BioSpectra's qualified water system. Quantity will be determined based on calculation referenced in process description using expected batch yield and concentration.	WFI Calculated Qty – 7000 L WFI lots used: E06DI01-020321 – 375.0 L E06DI01-020621 – 781.5 L E06DI01-020821 – 5793.5 L E06DI01-020921 – 48.0 L
Agitation	Agitation	Agitation will be performed according to the following conditions: 20 to 35 Hz for a minimum of 120 minutes prior to sample 1 and a minimum of 30 minutes prior to sample 2.	Sample 1: Agitation Rate – 29.70Hz Agitation Time – 129 minutes Normality - 1.01N Sample 2: Agitation Rate – 29.70Hz Agitation Time – 32 minutes Normality - 1.00N
Final Normality Adjustment (if required)	Calculate Adjustment Volume of WFI or NaOH 10N	Calculated final adjustment volume of WFI or NaOH 10N to achieve desired concentration.	No adjustment required
	Agitation	Agitation will be performed according to the following conditions: 20 to 35 Hz for a minimum of 120 minutes prior to sample 1 and a minimum of 30 minutes prior to sample 2.	No adjustment required
	0.95-1.05N	Confirmation of final product homogeneity verification based on two consecutive passing results.	No adjustment required
Sterile Fill/Packaging	Sterile Filtration	Sterile filtered through a 0.2 Micron STyLUX® ST0.2 UltraCap ® H.D. Filter.	Sterile filtered through a 0.2 Micron STyLUX® ST0.2 UltraCap ® H.D. Filter.
	Packaging	Packaging and testing of the finished product.	Packaged according to batch record and tested by Quality Control.

TABLE 5: TEMPORARY OPERATING INSTRUCTION (TOI) REVIEW

Control Number	Description	Impact
BTOI21-26	Re-printing of the batch record and transcribing raw data from the original batch record which was contaminated with product.	There was no impact to the validation study.

11. INVESTIGATION REVIEW:

There were two discrepancy investigations issued during or as a result of the manufacture of the validation batch. There was one discrepancy investigation issued in relation to the execution of the validation study.

TABLE 6: INVESTIGATION REVIEW

Control Number	Description	Impact
BDI21-43	Incorrect pre-process room inspection checklist was issued and completed for the manufacturing of the validation batch. All applicable inspection items were included on the printed checklist with the exception of the tube welder.	There was no impact to the quality of the batch or the validation study.
BDI21-44	Time continuity of the packaging steps for tote 4 and 6.	There was no impact to the quality of the batch or the validation study.
BDI24-78	The validation protocol referenced the FMEA, process flow diagram and process mapping diagram for NaOH 0.5N, there were no documents created and approved for NaOH 1N.	There was no impact to the validation study.

12. SAMPLE COLLECTION AND ANALYSIS:

All testing samples were collected and tested as stated in the protocol. Table 7 reflects the critical quality attributes as identified in the validation protocol. Tables 8-10 summarize the results obtained for the required analyses listed as listed in the tables for the validation batch.

The Degradation and impurity profile was not required for the purpose of this validation study and will reference the impurity profile report from the NaOH 10N Solution validation, BSI-RPT-0447 (historical DCN: 19-002737). The validation lot of Sodium Hydroxide 1N Solution was placed on the stability program for a real time stability study.

TABLE 7: CRITICAL QUALITY ATTRIBUTES (CQA)

CQA	SPECIFICATION
Normality (Concentration)	0.9 to 1.1N

TABLE 8: BATCH 1 RAW MATERIAL RESULTS

ANALYSIS	SPECIFICATION	RAW MATERIAL LOTS		
		NH4100-049-0720	NH4100-071-1020	NH4100-079-1120
Appearance and Color	Clear/ Colorless Liquid	Clear/ Colorless Liquid	Clear/ Colorless Liquid	Clear/ Colorless Liquid
Chloride	≤ 5 ppm	< 5 ppm	< 5 ppm	< 5 ppm
Endotoxins	≤ 2.0 EU/mL	< 0.5 EU/mL	< 0.6 EU/mL	< 0.5 EU/mL
Heavy Metals (Pb)	≤ 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm
Iron (Fe)	≤ 2 ppm	< 2 ppm	< 2 ppm	< 2 ppm
Normality	9.9 to 10.1N	10.1 N	10.0 N	10.0 N
Sodium Carbonate	≤ 0.6%	0.1 %	0.1 %	0.1 %

TABLE 9: BATCH 1 IN PROCESS RESULTS

ANALYSIS	SPECIFICATION	LOT NUMBER: NH3153-001-0221-PV
Normality	0.95N to 1.05N	Sample 1: 1.01N Sample 2: 1.00N

TABLE 10: BATCH 1 COMPOSITE AND UNIFORMITY TESTING

ANALYSIS	SPECIFICATION	LOT NUMBER: NH3153-001-0221-PV			
		COMPOSITE	BEGINNING TOTE 1	MIDDLE TOTE 3	END TOTE 6
Appearance and Color	Clear/ Colorless Liquid	Clear/ Colorless Liquid	Clear/ Colorless Liquid	Clear/ Colorless Liquid	Clear/ Colorless Liquid
Chloride	≤ 5 ppm	< 5 ppm	< 5 ppm	< 5 ppm	< 5 ppm
Endotoxins	≤ 2.0 EU/mL	< 0.5 EU/mL	< 0.5 EU/mL	< 0.5 EU/mL	< 0.5 EU/mL
Heavy Metals (Pb)	≤ 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm
Iron (Fe)	≤ 0.5 ppm	< 0.5 ppm	< 0.5 ppm	< 0.5 ppm	< 0.5 ppm
Normality	0.9 to 1.1N	1.0N	1.0N	1.0N	1.0N

13. CONCLUSION:

BioSpectra has validated the Sodium Hydroxide 1N Solution Bio Excipient Grade manufacturing process. All process suite equipment and utilities utilized for the Sodium Hydroxide 1N Solution validation were considered qualified and approved for use. All calibration records for critical instruments have been recorded and verified throughout the executed batch records, see Table 2 Manufacturing Instrumentation Calibration Verification. The manufacturing personnel were trained on the batch record prior to manufacturing the validation batch. The discrepancies encountered during the manufacture of the validation batch had no impact on the validation, reference Section 11: Investigation Review. The Critical Process Parameters were met, the documentation of the parameters are listed in Section 10, Manufacturing Observations. The Finished Goods Analysis met the specifications as listed in the protocol, the testing results are in Section 12: Sample collection and analysis.

The Sodium Hydroxide 1N Solution manufacturing process in Process Room M03 is validated to be compliant with key compliance grades up to and including Bio Excipient grade. The Sodium Hydroxide 1N Solution Bio Excipient Grade manufacturing process in Process Room M03 is an approved Bio Excipient Grade manufacturing process performed in accordance with ICH Q7 Good Manufacturing Practice Guidance. All expectations of the validation have been met and approved. The results contained in this validation report deem Sodium Hydroxide 1N Solution Bio Excipient Grade manufactured, using Sodium Hydroxide 1N Bio Excipient Grade Batch Record, DCN: BSI-MPR-0041, to be a validated process, suitable for use as an Excipient.