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31-May-2021	12:40:03 PM	QUALITY	McCollian, Carissa K

BioSpectra Validation External Report

Validation Report for the Manufacture of:

L-Cysteamine diHCl (2-MEA)

To be Manufactured as the Following Codes:

CSMH-3200 through CSMH-32XX

To be Manufactured at:

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

In Compliance with the Standards of:

ICH Q7 Good Manufacturing Practice Guide

Manufactured to be Suitable for use as:

Excipient

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1. INTRODUCTION

The Validation of a manufacturing process used to produce Excipients is a requirement under ICH Q7 Good Manufacturing Practice Guide. This validation protocol describes the process as performed using, Process Suite N05 of Zone N of the Bangor, PA facility. This process Suite is intended to manufacture excipients in accordance with ICH Q7. The FDA defines validation, specifically process validation as:

"The collection and evaluation of data, from the process design state through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product."

This L-Cysteamine HCl (2-MEA) Validation Study was a prospective validation to ensure that the L-Cysteamine HCl (2-MEA) process conforms to the pre-established critical process parameters associated with the process. This prospective validation study should be completed before the release of the validation batch for commercial distribution, based on approval of the executed batch record, documented evidence that the batch conforms to the finished goods specifications and this validation report. The validation study will be considered complete for release of the validation batches upon the approval of this report. This validation required three batches of L-Cysteamine HCl (2-MEA) to be manufactured.

2. OBJECTIVE

The objective of this Validation Summary Report is to verify and assure that the manufacturing process for L-Cysteamine HCl (2-MEA) consistently produces material that meets a set of pre-determined specifications as listed in Table 4 or indicates that the material will require Phase 2 processing. This validation was performed as this is a new manufacturing process established by BioSpectra.

This validation included three batches of 2-MEA, manufactured according to the current revision of the Batch Record. This validation report will summarize the manufacture of the validation batches within the validation study. As stated in the protocol, representative samples were submitted to the QC Laboratory and were tested against Finished Good specifications. This was conducted to verify that the process is capable of consistently producing material that meets Finished Good Specifications.

3. SCOPE:

This Report applies to the validation batches of 2-MEA, Bio Excipient Grade, within this validation study. This batch process includes the following process steps: mother liquor creation or

verification, raw material charge, purification, cooling/recrystallization, crystal separation via funnel filter, tray drying, packaging and testing of the finished good, release to Phase 2 processing as needed. Specifications and approval requirements for all Raw Materials (RM) and components have been created; therefore, these RM and components are not covered by this Report except that only approved RM and components were used.

4. EXECUTIVE SUMMARY

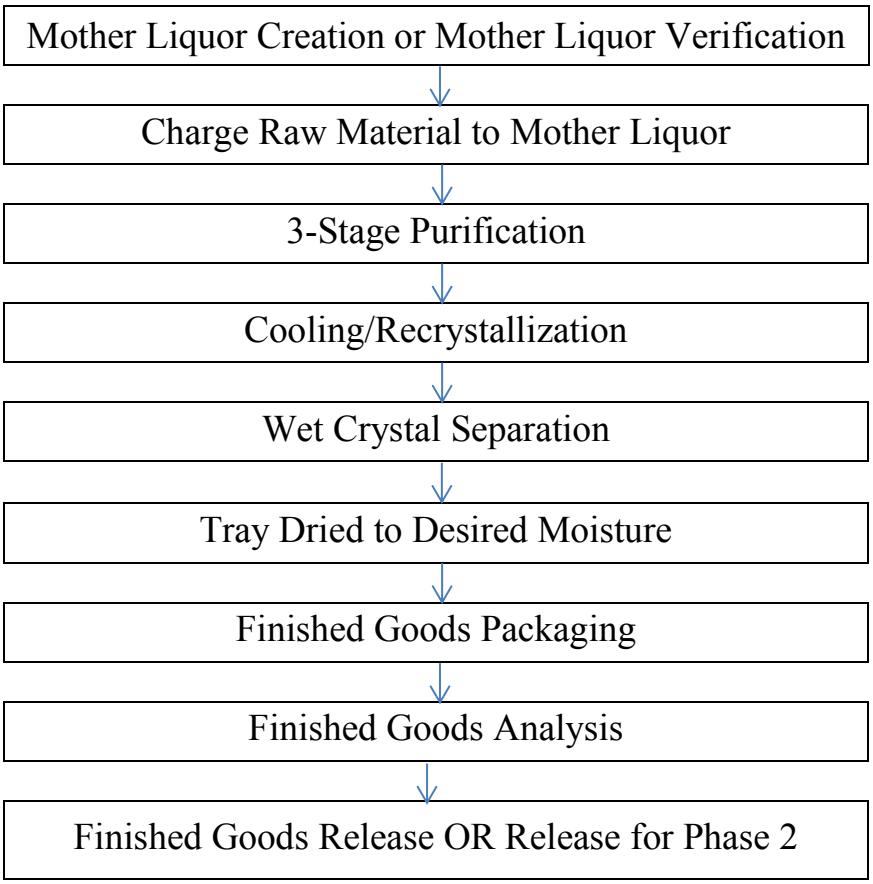
The Validation Study for L-Cysteamine HCl (2-MEA) was performed due to the start of a new process for this material.

The L-Cysteamine HCl (2-MEA) manufacturing process is a manufacturing/purification process with Critical Process Parameters as detailed in the Validation Protocol. The CPP were developed based on the FMEA analysis conducted for the process and were found to be in accordance with BioSpectra's Manufacturing Process Validation Master Plan. The utilities and process used in the manufacture of this product have been qualified in accordance with BioSpectra's Equipment Qualification Master Plan. The manufacturing of validation batches for this validation study was deemed successful and finished goods batches will be released in accordance with the Validation plan and the approval of all related manufacturing and QC documentation.

5. PROCESS FLOW DIAGRAM

L-CYSTEAMINE HCL (2-MEA) PROCESS FLOW DIAGRAM

PHASE 1 PROCESSING



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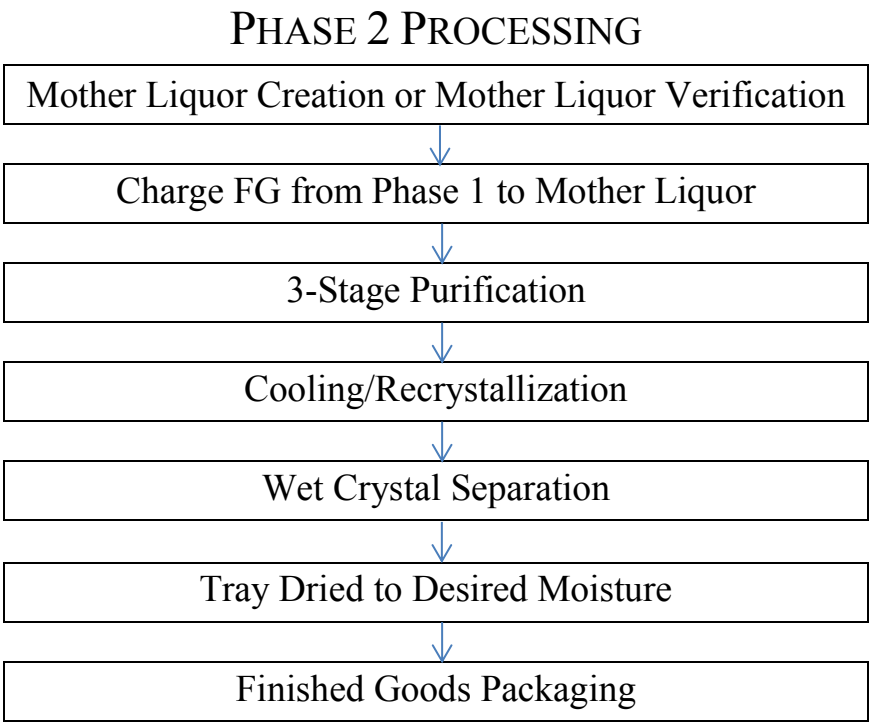

6. MANUFACTURING OBSERVATIONS

The L-Cysteamine HCl (2-MEA) batch that was manufactured in accordance with the current L-Cysteamine HCl (2-MEA) Bio Excipient Grade Batch Record DCN: 21-001788 and has met the requirements and acceptance criteria detailed in the Validation protocol. The manufacturing observations for all batches of material are listed in Tables 1-3 below.

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TABLE 1: MANUFACTURING OBSERVATIONS

Process Step/Additional Analysis	Acceptance Criteria	Validation Batch 1:
Batch Charge L-Cysteamine HCl RM	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria
Filtration	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria
Crystallization	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria
Wet Crystal Wash	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria
Drying	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria

TABLE 2: MANUFACTURING OBSERVATIONS

Process Step/Additional Analysis	Acceptance Criteria	Validation Batch 2:
Batch Charge L-Cysteamine HCl RM	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria
Filtration	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria
Crystallization	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria
Wet Crystal Wash	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria
Drying	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria

TABLE 3: MANUFACTURING OBSERVATIONS

Process Step/Additional Analysis	Acceptance Criteria	Validation Batch 3:
Batch Charge L-Cysteamine HCl RM	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria
Filtration	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria
Crystallization	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria
Wet Crystal Wash	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria
Drying	As stated in the Batch Record and Validation Protocol	Met Acceptance Criteria

7. ANALYSIS

The L-Cysteamine HCl (2-MEA) batches manufactured in accordance with the current L-Cysteamine HCl (2-MEA) Bio Excipient Grade Batch Record DCN:21-001788 v.1.0 has met the BioSpectra analytical requirements associated with Current Code: CSMH-3250 or Phase I Analysis. The results can be found in Table 4. Uniformity Analysis will be reported within the final internal Validation Report. All required analyses were completed in accordance with Table 5 and met specification, actual results will be reported on within the final internal validation report.

TABLE 4: COMPOSITE FINISHED GOODS TESTING RESULTS

Finished Goods Analysis	Specification CSMH-3250	Validation Batch 1: CSMH-0121-00003-PV (released to Phase 2 Processing)	Validation Batch 2: CSMH-0121-00006-PV	Validation Batch 3: CSMH-0121-00007-PV
Appearance and Color	White or colorless crystals or powder, may contain lumps	White or colorless crystals or powder, may contain lumps	White or colorless crystals or powder, may contain lumps	White or colorless crystals or powder, may contain lumps
Appearance of Solution	Colorless, clear solution	Colorless, clear solution	Colorless, clear solution	Colorless, clear solution
Argentometric Titration	30.6 – 31.8%	31.3%	31.0%	31.1%
Assay (HPLC Weight %)	98.0 – 102.0%	100.0%	100.5%	100.1%
Bioburden	≤ 100 CFU/g	<100 CFU/g	<100 CFU/g	<100 CFU/g
Endotoxin	≤ 50 EU/g	<40 EU/g	<40 EU/g	<40 EU/g
HPLC Minor Component 1 (Area %)	Cystamine ≤ 2.0%	1.0%	0.5%	1.2%

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Finished Goods Analysis		Specification CSMH-3250	Validation Batch 1: CSMH-0121-00003-PV (released to Phase 2 Processing)	Validation Batch 2: CSMH-0121-00006-PV	Validation Batch 3: CSMH-0121-00007-PV
Heavy Metals		≤ 20 mg/kg (ppm)	< 20 ppm	< 20 ppm	< 20 ppm
Identification (IR)		Conforms to reference standard	Conforms to reference standard	Conforms to reference standard	Conforms to reference standard
Loss on Drying		≤ 1.0%	0.5%	0.2%	0.1%
Trace Metal Analysis (ICP)	Aluminum (Al)	≤ 5 ppm	< 0.80 ppm	< 0.80 ppm	< 0.80 ppm
	Arsenic (As)	≤ 1 ppm	< 0.03 ppm	< 0.03 ppm	< 0.03 ppm
	Barium (Ba)	≤ 5 ppm	< 1.4 ppm	< 1.4 ppm	< 1.4 ppm
	Bismuth (Bi)	≤ 5 ppm	< 0.40 ppm	< 0.40 ppm	< 0.40 ppm
	Calcium (Ca)	≤ 10 ppm	10 ppm	3.4 ppm	< 1.5 ppm
	Cadmium (Cd)	≤ 1 ppm	< 0.004 ppm	< 0.004 ppm	< 0.004 ppm
	Cobalt (Co)	≤ 1 ppm	< 0.01 ppm	< 0.01 ppm	< 0.01 ppm
	Chromium (Cr)	≤ 1 ppm	< 0.10 ppm	< 0.10 ppm	0.12 ppm
	Copper (Cu)	≤ 1 ppm	0.17 ppm	0.09 ppm	0.11 ppm
	Iron (Fe)	≤ 1 ppm	0.72 ppm	< 0.40 ppm	0.71 ppm
	Mercury (Hg)	≤ 1 ppm	0.45 ppm	0.36 ppm	0.49 ppm
	Potassium (K)	≤ 50 ppm	< 4.0 ppm	< 4.0 ppm	< 4.0 ppm
	Lithium (Li)	≤ 5 ppm	< 0.50 ppm	< 0.50 ppm	< 0.50 ppm
	Magnesium (Mg)	≤ 5 ppm	< 0.40 ppm	< 0.40 ppm	< 0.40 ppm
	Manganese (Mn)	≤ 1 ppm	0.15 ppm	< 0.05 ppm	< 0.05 ppm
	Molybdenum (Mo)	≤ 5 ppm	< 0.10 ppm	< 0.10 ppm	< 0.10 ppm
	Sodium (Na)	≤ 50 ppm	83 ppm	22 ppm	5.1 ppm
	Nickel (Ni)	≤ 1 ppm	0.09 ppm	< 0.04 ppm	0.05 ppm
	Lead (Pb)	≤ 1 ppm	0.03 ppm	0.02 ppm	0.03 ppm
	Antimony (Sb)	≤ 1 ppm	< 0.18 ppm	< 0.18 ppm	< 0.18 ppm
	Selenium (Se)	≤ 1 ppm	< 0.10 ppm	< 0.10 ppm	< 0.10 ppm
	Strontium (Sr)	≤ 5 ppm	< 0.40 ppm	< 0.40 ppm	< 0.40 ppm
	Vanadium (V)	≤ 1 ppm	< 0.02ppm	< 0.02ppm	< 0.02ppm
	Zinc (Zn)	≤ 1 ppm	< 0.40 ppm	< 0.40 ppm	< 0.40 ppm
Purity (HPLC Area %)		≥ 98.0%	98.9%	99.5%	98.8%
Purity (Cysteamine (HPLC))		≥ 92.0%	98.9%	99.5%	98.8%
		≤8.0% related substances	1.1%	0.5%	1.2%
Residual Solvents	Ethanol	≤ 5000 ppm	< 2500 ppm	< 2500 ppm	< 2500 ppm
	Isopropyl Alcohol (IPA)	≤ 5000 ppm	3853 ppm	3151 ppm	< 2500 ppm
	Tert-Butylmethyl Ether	≤ 5000 ppm	< 2500 ppm	< 2500 ppm	< 2500 ppm
Solubility		Clear and Colorless	Clear and Colorless	Clear and Colorless	Clear and Colorless

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TABLE 5: VALIDATION REQUIRED ANALYSES

Required Analysis	Specification
Approved Raw Material	
Approved Raw Material (RM) Microbial Analysis	Monitor for TAMC/TYMC, Escherichia coli, Pseudomonas aeruginosa, Salmonella species, Staphylococcus aureus
Approved Raw Material (RM) Endotoxin Analysis	Monitor
Mother Liquor	
Mother Liquor (ML) Microbial Analysis	Monitor for TAMC/TYMC, Escherichia coli, Pseudomonas aeruginosa, Salmonella species, Staphylococcus aureus
Mother Liquor (ML) Endotoxin Analysis	Monitor
Wet Crystals	
Wet Crystal (WC) Microbial Analysis	Monitor for TAMC/TYMC, Escherichia coli, Pseudomonas aeruginosa, Salmonella species, Staphylococcus aureus
Wet Crystal (WC) Endotoxin Analysis	Monitor
Finished Goods	
Finished Good (FG) Dry Crystal Moisture Content	0.10% maximum via MF-50 Moisture Balance
Finished Goods (FG) Quality Control Analysis	Refer to Bulk Summary Sheet, DCN: 21-003968
Finished Good (FG) Stability Testing Long Term: 2-8°C Accelerated: 23-27°C	All validation lots shall be placed in the stability program.
Degradation and Impurity Profile	Meets Requirements, DCN: 21-003748

8. ADDITIONAL INFORMATION

8.1. Degradation and Impurity Profile

8.1.1. A Degradation and Impurity profile was performed for this validation. The degradation and impurity profile will be reported on in the Degradation and Impurity Profile Report and referenced in the final internal validation report

8.2. Stability Study

8.2.1. The Stability Analysis for L-Cysteamine HCl (2-MEA) consists of an evaluation of the following analyses detailed in Table 6. These analyses were selected based on a combination finished goods requirements and Stability Indicating Protocol. The analyses listed below will be performed for each validation batch and 1 batch per year

manufactured. Each batch placed on the Long-Term Stability Program will undergo stability analysis at intervals 0, 3, 6, 9, 12, 18, 24, 36, 48, and 60-month.

TABLE 6: STABILITY ANALYSIS

Analysis	Stability Specification
Assay (HPLC Weight %)	98.0 – 102.0%
HPLC Minor Component 1 (Area %)	Cystamine ≤ 2.0%
Purity (HPLC Area%)	≥ 98.0%
Purity (Cysteamine(HPLC))	≥ 92.0%
	≤ 8.0% related substances
Appearance and Color	White or colorless crystals or powder, may contain lumps
Chloride	30.6-31.8%
Identification (IR)	Passes Test
Loss on Drying	≤ 1.0%

9. CONCLUSION

BioSpectra has manufactured and validated the 2-MEA process to be compliant with key compliance grades up to and including the Bio Excipient grade. This Bio Excipient Grade classification requires that the excipient be manufactured in accordance with ICH Q7 GMP guidelines to be suitable for use as a GMP manufactured Excipient. The results obtained during this validation study and subsequent analysis provide evidence that the L-Cysteamine HCl (2-MEA) manufactured using the approved process will consistently meet the approved specifications. The utilities and process used in the manufacture of this product have been qualified in accordance with BioSpectra's Equipment Qualification Master Plan. The results reported from the validation batches of L-Cysteamine HCl (2-MEA) for this Validation Study provided the evidence necessary confirm that the developed process for L-Cysteamine HCl (2-MEA) produces acceptable material. The L-Cysteamine HCl (2-MEA) manufacturing process, using Process Suite N05, can be considered an approved, validated process capable of consistently producing Bio Excipient Grade material that meets Finished Good Specifications.

All Raw Materials used for the processing of L-Cysteamine HCl (2-MEA) were approved before use in accordance with RM specifications. The Validation samples of L-Cysteamine HCl (2-MEA) will be placed into Long Time Stability and will be reported on annually. The data obtained from the Stability Study will be utilized to establish a retest date.

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