BIOBUFFER SOLUTIONS

100 Majestic Way, Bangor, PA 18013 / www.biospectra.us

BioBuffer Solutions Validation Summary

Validation summary for the manufacture of:

L-Histidine Monochloride Monohydrate,
Bio Pharma Grade for BioBuffer Solutions Product Line

Manufactured as the following codes:

L-Histidine Monochloride Monohydrate LHMM-42XX
or Below Grades

Manufactured By:

Approved Global Supply Chain

In compliance with the standards of:

Approved Supplier's ISO 9001:2015
Certified Management System

Manufactured to be suitable for use as:

Process Chemical

TABLE OF CONTENTS

1. INTRODUCTION:

L-Histidine Monochloride Monohydrate, Bio Pharma Grade for BioBuffer Solutions Product line is manufactured and validated by the Approved Supplier in accordance with their ISO 9001:2015 certified management system. This validation summary is applicable to the validation study conducted by the Approved Supplier to ensure that the process used for manufacturing L-Histidine Monochloride Monohydrate is sufficient to produce material of consistent quality and yield that meets its predetermined specifications.

The L-Histidine Monochloride Monohydrate Validation Study consisted of three prospective validation batches to ensure that the L-Histidine Monochloride Monohydrate manufacturing process conforms to the predetermined specifications and quality attributes. The material was manufactured utilizing approved raw materials, as well as qualified and calibrated manufacturing equipment. Calibrated Quality Control instruments were utilized in the analysis of the material. There were no deviations or out of specifications observed during the validation activity.

2. OBJECTIVE:

The objective of this Validation Report is to verify and assure that the manufacturing process for L-Histidine Monochloride Monohydrate at the Approved Supplier in India consistently produces material that meets a set of pre-determined specifications and quality attributes as listed in Table 1.

The Validation batches of L-Histidine Monochloride Monohydrate were manufactured according to the current version of the Batch Record. Once the manufacture of the batches was completed, 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 manufacturing process for L-Histidine Monochloride Monohydrate, Bio Pharma Grade for BioBuffer Solutions Product line which includes the following process steps: Synthetic Reaction, Purified Water Wash, Filtration, Drying and Testing of the Finished Goods.

4. REFERENCES:

4.1. BSI-FRM-1213, Raw Material Evaluation Request Form – L-Histidine Monochloride Monohydrate

4.2. BSI-MEM-1233, L-Histidine Monochloride Monohydrate Raw Material Evaluation Result Summary

4.3. BSI-RPT-1745, Analytical Method Verification Report: L-Histidine Monochloride Monohydrate Water Determination via Karl Fischer Utilizing Metrohm 907 Auto Titrator

4.4. BSI-RPT-1746, Analytical Method Validation Report: L-Histidine Monochloride Monohydrate Assay by Potentiometric Titration with 0.1N Sodium Hydroxide

4.5. BSI-SOP-0056, Materials Handling SOP

4.6. BSI-SOP-0057, Supplier, Manufacturer, and Service Provider Qualification Master Plan

5. EXECUTIVE SUMMARY:

The L-Histidine Monochloride Monohydrate manufacturing process is a validated manufacturing process with Process Parameters as detailed in the Batch Record. The L-Histidine Monochloride Monohydrate manufacturing process includes adding N-Boc L-Histidine and Purified Water to the Reactor. Once combined, the solution is stirred at a specified temperature followed by the addition of Concentrated Hydrochloric Acid. The solution is then stirred at a specified temperature for a required timeframe. Next, 10% NaOH Solution is added to achieve the pH specification. The material is distilled to form a white slurry concentrated mass. It is then separated via Centrifuge and dried utilizing Rotary Vacuum Dryer at a specified temperature and time duration to meet an in-process Moisture Content specification of NMT 0.50%. The approved material is then final packaged and released. BioSpectra receives the material, then samples and tests the material to complete Finished Good Disposition in accordance with the Materials Handling Procedure.

6. PROCESS FLOW DIAGRAM:

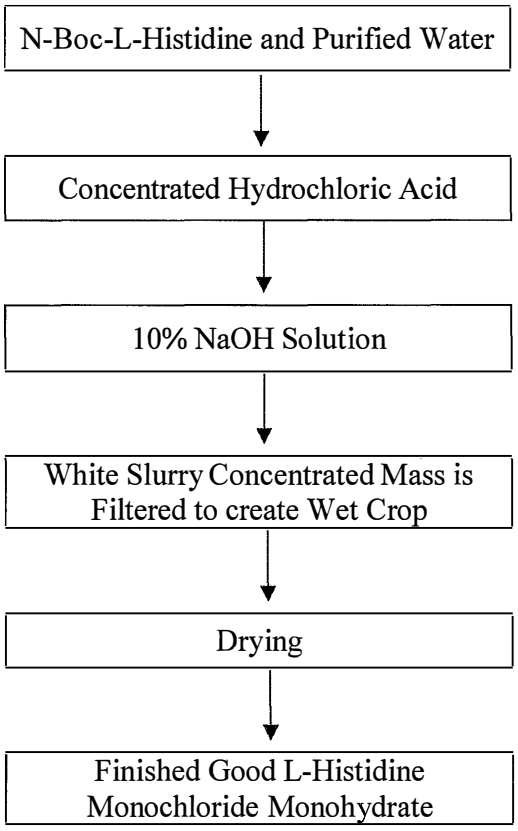

FIGURE 1. PROCESS FLOW DIAGRAM

7. ANALYSIS:

The L-Histidine Monochloride Monohydrate validation batches were manufactured in accordance with the Approved Supplier's current L-Histidine Monochloride Monohydrate Batch Record and have met the analytical requirements associated with the material sold for use as Bio Pharma Grade for BioBuffer Solutions Product line for product codes LHMM-4250. The analytical results for the critical quality attributes (CQA) of the three validation batches have met specification as reported by the Approved Supplier. All in-process and release analyses were also met as required in the validation study and for release to BioSpectra. BioSpectra's Quality Control Laboratory has performed Supplier Qualification Testing, as detailed in BSI-MEM-1233, L-Histidine Monochloride Monohydrate Raw Material Evaluation Result Summary. BioSpectra's Quality Control Laboratory has additionally analyzed the Finished Good Results for release to LHMM-4250, which are detailed in Table 1.

TABLE 1. LHMM-4250 VALIDATION RESULTS

Analysis		Specification	Batch 1 Results	Batch 2 Results	Batch 3 Results
Ammonium (EP, JP)		≤ 0.02%	< 0.02%	< 0.02%	< 0.02%
Appearance and Color		White or colorless, crystalline powder crystals	White Crystalline Powder or Crystals	White Crystalline Powder or Crystals	White Crystalline Powder or Crystals
Appearance of Solution (EP)		Passes Test	Passes Test	Passes Test	Passes Test
Assay (Dried Substance)		98.5% - 101.0%	99.8%	100.3%	100.2%
Assay (Anhydrous basis)		99.0% - 101.0%	99.9%	99.7%	99.9%
Bioburden		≤ 100 CFU/g	< 100 CFU/g	< 100 CFU/g	< 100 CFU/g
Clarity and Color of Solution (JP)		Clear and Colorless	Clear and Colorless	Clear and Colorless	Clear and Colorless
Endotoxin		≤ 100 EU/g	< 1 EU/g	< 1 EU/g	<1 EU/g
Identification Specific Optical Rotation (EP-A)		+9.2° to +10.6°	+ 9.9°	+ 9.9°	+ 9.9°
Identification B, pH (EP)		3.0 – 5.0	3.9 @ 23.0°C	4.0 @ 23.0°C	4.0 @ 23.0°C
Identification, IR (EP-C/JP-1)		Passes Test	Passes Test	Passes Test	Passes Test
Identification D (EP)		Passes Test	Passes Test	Passes Test	Passes Test
Identification E (EP)		Passes Test	Passes Test	Passes Test	Passes Test
Identification F (EP)		Passes Test	Passes Test	Passes Test	Passes Test
Identification 2 Chloride (JP)		Passes Test	Passes Test	Passes Test	Passes Test
Heavy Metals (JP)		≤10ppm	<0.15ppm	<0.15ppm	<0.15ppm
Iron (EP, JP)		≤ 10 ppm	< 6.0 ppm	< 6.0 ppm	< 6.0 ppm
Loss on Drying (EP)		7.0 – 10.0%	8.3%	8.7%	8.7%
Ninhydrin-positive Substances (EP)	Each Individual Impurity	≤ 0.2%	<0.2%	<0.2%	< 0.2%
	Total Impurities	≤ 0.5%	<0.5%	<0.5%	<0.5%
Optical Rotation (JP)		+9.2° to +10.6°	+ 9.9°	+ 10.0°	+9.9°
pH (JP)		3.5 – 4.5	4.0 @ 23.2°C	4.0 @ 23.2°C	4.0 @ 23.2°C
Related Substances (JP)		Passes Test	Passes Test	Passes Test	Passes Test
Residue on Ignition. Sulfated Ash (EP, JP)		≤ 0.1%	< 0.1%	< 0.1%	< 0.1%
Sulfates (EP)		≤ 300 ppm	< 300 ppm	< 300 ppm	< 300 ppm
Sulfates (JP)		≤ 280 ppm	< 280 ppm	< 280 ppm	< 280 ppm
Water (JP)		7.2 – 10.0%	8.3%	8.2%	8.4%

8. CONCLUSION:

The Approved Supplier has successfully manufactured and validated three batches of validated Bio Pharma Grade for BioBuffer Solutions Product line L-Histidine Monochloride Monohydrate to be compliant with key compliance grades up to and including the Bio Pharma Grade for BioBuffer Solutions Product line. This Bio Pharma Grade for BioBuffer Solutions Product line classification requires that a product be manufactured in accordance with the Approved Supplier's ISO 9001:2015 certified management system and is suitable for use as a process chemical. The results obtained in this validation summary deem L-Histidine Monochloride Monohydrate manufactured using this process acceptable. The equipment used in the manufacture of this product have been qualified in accordance with the Approved Supplier's ISO 9001:2015 certified management system. The validation samples of L-Histidine Monochloride Monohydrate were placed onto stability. All finished good samples analyzed for all three batches of this validation study met Finished Good Specifications for product code LHMM-4250 or below compliance grades.