BIOBUFFER SOLUTIONS

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

# BioBuffer Solutions
# External Validation Report

## Validation summary for the manufacture of:

L-Arginine HCl,
Bio Pharma Grade for BioBuffer Solutions Product Line

## Manufactured as the following codes:

L-Arginine HCl LARH-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

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## 1. INTRODUCTION:

L-Arginine HCl, 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 report is applicable to the validation study conducted by the Approved Supplier to ensure that the process used for manufacturing L-Arginine HCl is sufficient to produce material of consistent quality and yield that meets its predetermined specifications.

The L-Arginine HCl Validation Study consisted of three prospective batches to ensure that the L-Arginine HCl 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 specification results observed during the validation activity.

## 2. OBJECTIVE:

The objective of this Validation Report is to verify and assure that the manufacturing process for L-Arginine HCl by the Approved Supplier in India consistently produces material that meets a set of pre-determined specifications as listed in Table 1, as well as established quality attributes.

The Validation batches of L-Arginine HCl were manufactured according to the current version of the L-Arginine HCl 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-Arginine HCl, 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-ATM-0114, L-Arginine HCl Testing Methods
4.2. BSI-FRM-1212, Raw Material Evaluation Request Form – L-Arginine Hydrochloride
4.3. BSI-MEM-1207, L-Arginine Hydrochloride Raw Material Evaluation Result Summary
4.4. BSI-SOP-0056, Materials Handling SOP
4.5. BSI-SOP-0057, Supplier, Manufacturer, and Service Provider Qualification Master Plan
4.6. BSI-SOP-0576, BioBuffer Solutions Testing Program

4.7. BSI-SPC-0223, LARH-4220 L-Arginine HCl Bio Pharma Grade Specifications

## 5. EXECUTIVE SUMMARY:

The L-Arginine HCl manufacturing process is a validated manufacturing process with Critical Process Parameters as detailed in the Batch Record. The L-Arginine HCl manufacturing process includes adding Ethyl Acetate to N-Boc-L-Arg-HCl.$H_2O$ followed by a drop-wise addition of Ethyl Acetate HCl. Purified Water is added to the reactor followed by a slow addition of 10% NaOH solution. The Reaction Mass undergoes two in-process control analyses, which include TLC with specification SM should be Nil, and pH with a specification of 5.5-5.7. The reactors include Equipment ID: GLR-101/102 and GLR-207. A Purified Water Wash is performed followed by filtration via Centrifuge Equipment ID: SCF-201 to produce a Wet Cake. The Wet Cake undergoes Rotary Vacuum Drying using Equipment ID: RVD-201 with an in-process Moisture Content specification of NMT 0.50% followed by final packaging, testing, and shipment to BioSpectra. BioSpectra personnel receive the material followed by sampling, analysis, and Finished Good Disposition in accordance with the Materials Handling Procedure.

## 6. PROCESS FLOW DIAGRAM:

The following Process Flow Diagram details the L-Arginine HCl manufacturing process.

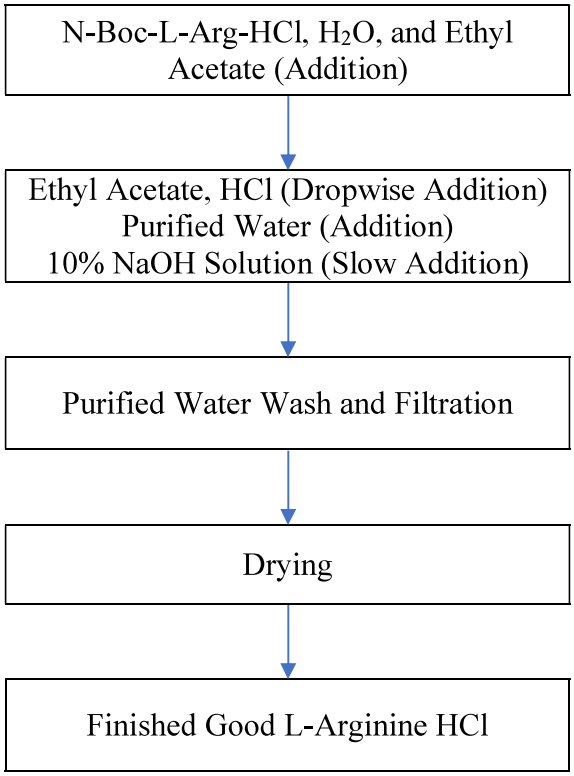


**FIGURE 1. PROCESS FLOW DIAGRAM**

## 7. ANALYSIS:

The L-Arginine HCl validation batches were manufactured in accordance with the Approved Supplier's current L-Arginine HCl 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 code LARH-4220. 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 specifications 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-1207, L-Arginine Hydrochloride Raw Material Evaluation Result Summary. BioSpectra's Quality Control Laboratory has additionally analyzed the Finished Good Results for release to LARH-4220, which are detailed in Table 1.

**TABLE 1. LARH-4220 VALIDATION RESULTS**

| Analysis | Specification | Batch 1 Results | Batch 2 Results | Batch 3 Results |
|---|---|---|---|---|
| Appearance | White or almost white crystalline powder or colourless crystals | White Crystalline Powder | White Powder | White Powder |
| Ammonium (EP/JP) | ≤ 0.02% | < 0.02% | < 0.02% | < 0.02% |
| Appearance of Solution (EP) | Clear, Colourless Solution | Clear, Colourless Solution | Clear, Colourless Solution | Clear, Colourless Solution |
| Arsenic (JP) | ≤ 2 ppm | < 0.45 ppm | < 0.45 ppm | < 0.45 ppm |
| Assay (dried basis) (USP/EP/JP) | 98.5 – 101.0% | 99.8% | 100.1% | 100.0% |
| Chloride Content (USP) | 16.5 – 17.1% | 16.9% | 16.8% | 16.9% |
| Clarity and Color of Solution (JP) | Passes Test | Passes Test | Passes Test | Passes Test |
| Heavy Metals (JP) | ≤ 20 ppm | < 0.15 ppm | < 0.15 ppm | < 0.15 ppm |

| Analysis | | Specification | Batch 1 Results | Batch 2 Results | Batch 3 Results |
|---|---|---|---|---|---|
| Identification, IR (USP-A/EP-B/JP-1) | | Conforms to Reference Standard | Conforms to Reference Standard | Conforms to Reference Standard | Conforms to Reference Standard |
| Identification, Specific Optical Rotation (EP-A/USP/JP) | | +21.5° to +23.5° | +22.6° | +22.6° | +22.6° |
| Identification C, TLC (EP) | | Passes Test | Passes Test | Passes Test | Passes Test |
| Identification D, Color (EP) | | Passes Test | Passes Test | Passes Test | Passes Test |
| Identification, Chlorides (EP-E/JP-2) | | Passes Test | Passes Test | Passes Test | Passes Test |
| Iron (EP) | | ≤ 10 ppm | 2.0 ppm | 2.7 ppm | 2.4 ppm |
| Loss on Drying (USP/EP/JP) | | ≤ 0.20% | 0.12% | 0.04% | 0.05% |
| Ninhydrin-Positive Substances (USP/EP) | Each Individual Impurity | ≤ 0.2% | < 0.2% | < 0.2% | < 0.2% |
| | Total Impurities | ≤ 0.5% | < 0.5% | < 0.5% | < 0.5% |
| pH (1 in 10) (JP) | | 4.7 – 6.2 | 5.5 | 5.6 | 5.6 |
| Related Substances (USP/JP) | | Passes Test | Passes Test | Passes Test | Passes Test |
| Residue on Ignition, Sulfated Ash (USP/EP/JP) | | ≤ 0.1% | < 0.1% | < 0.1% | 0.1% |
| Sulfate (USP/EP/JP) | | ≤ 0.028% | < 0.028% | < 0.028% | < 0.028% |

## 8. CONCLUSION:

The Approved Supplier has successfully manufactured and validated three batches of Bio Pharma Grade for BioBuffer Solutions Product line L-Arginine HCl 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 report deem L-Arginine HCl manufactured using this process acceptable. The equipment used in the manufacture of this product has been qualified in accordance with the Approved Supplier's ISO 9001:2015 certified management system, and all calibration records for critical instruments have been documented and verified. The validation samples of L-Arginine HCl were placed onto stability. All finished good samples analyzed for all three batches of this validation study met Finished Good Specifications for product code LARH-4220 or below compliance grades.