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BIOSPECTRA

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BioSpectra Validation External Report

Validation Report for the Manufacture of:

GUANIDINE HCL 6M SOLUTION

To be Manufactured as the Following Codes:

GHCL-3100 OR BELOW GRADE

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 (considered a revalidation) protocol describes the process as performed using, Process Suite L09 of Zone L at 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 Guanidine HCl 6M Solution Validation Study was a concurrent validation to ensure that the Guanidine HCl 6M Solution process conforms to the pre-established critical process parameters and to verify and assure that the manufacturing process for GHCl 6M Solution, Bio Excipient is controlled in a validated state after the process was moved from the BioSpectra, Stroudsburg, PA facility to the BioSpectra Bangor, PA facility. This concurrent validation study allows for the release of the validation batch for commercial distribution based on approval of the executed batch record and documented evidence that the batch conforms to the finished goods specifications before release. This validation required three batches of Guanidine HCl 6M Solution to be manufactured.

2. OBJECTIVE

The objective of this External Validation Report is to summarize the events of the validation study used to verify and assure that the manufacturing process for Guanidine HCl 6M Solution consistently produces material that meets a set of pre-determined specifications as listed in Table I. This validation was performed due to process suite change in order to ensure the process is in a validated state.

This validation included 3 batches of Guanidine HCl 6M Solution, manufactured according to the current revision of the Batch Record. This validation report will summarize the manufacture of the three 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 all validation batches of Guanidine HCl 6M Solution, Bio Excipient Grade, within this validation study. This batch process includes the following process steps: Purified Water and Raw Material Charge, 2 Step Purification, pH/molarity Adjustment (if needed) and Final Filtration to

Packaging. 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.

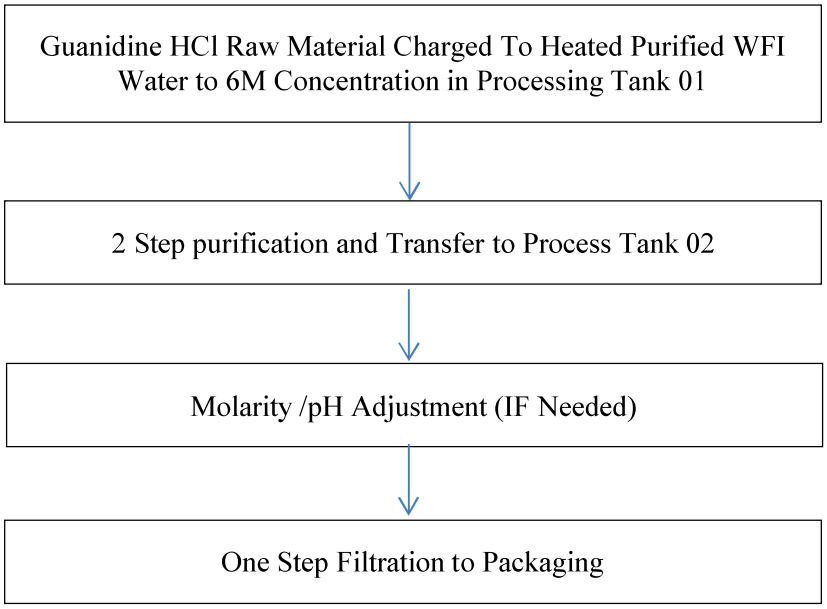
4. EXECUTIVE SUMMARY

Guanidine Hydrochloride 6M Solution will be manufactured in Process Room L09 located in Zone L of BioSpectra's Bangor, PA facility. Process Room L09 is a dedicated manufacturing room for producing Guanidine Hydrochloride 6M Solution. The Guanidine Hydrochloride 6M Solution process was manufactured at the BioSpectra's Stroudsburg, PA facility and will now be manufactured at the Bangor, PA facility using equivalent materials and equipment as the validated process in Stroudsburg, PA and performed in accordance with ICH Q7 guidelines. The process steps include: Purified Water and Raw Material Charge, 2 Step Purification, pH/molarity Adjustment (if needed), and Final Filtration to Packaging.

The Guanidine HCl 6M Solution 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 the validation batches for this validation study was deemed successful and the batches were released in accordance with the Validation plan and the approval of all related manufacturing and QC documentation.

5. PROCESS FLOW DIAGRAM

GUANIDINE HCL 6M SOLUTION
PROCESS FLOW DIAGRAM



6. MANUFACTURING OBSERVATIONS

The Guanidine HCl 6M Solution batches were manufactured in accordance with the current Guanidine HCl 6M Solution Bio Excipient Grade Batch Record DCN:20-001778 and have met the requirements. The manufacturing observations for each batch is listed in Table 1 below.

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TABLE 1: MANUFACTURING OBSERVATION FOR VALIDATION BATCHES

Process Step/ Additional Analysis	Acceptance Criteria	Validation Batch 1: GH3100-026-0221-PV	Validation Batch 2: GHCL-0121-00008-PV	Validation Batch 3: GHCL-0121-00012-PV	Previously Validated Batch GH7100-012-1117-PV
Batch Creation: Raw Material Charge	Charge material to build solution of required 6M concentration for Purification	Material charged to build desired solution concentration of 6M Guanidine HCl Solution was prepared for purification	Material charged to build desired solution concentration of 6M Guanidine HCl Solution was prepared for purification	Material charged to build desired solution concentration of 6M Guanidine HCl Solution was prepared for purification	Material charged to build desired solution concentration of 6M Guanidine HCl Solution was prepared for purification
Purification	Purify using 2-Step purification.	Purified Using the 2-step purification	Purified Using the 2-step purification	Purified Using the 2-step purification	Purified Using the 2-step purification
Packaging	Final Filter before packaging. Final Batch Yield	Final Filter Packaging completed Batch Yield 95.5%	Final Filter Packaging completed Batch Yield 97.34%	Final Filter Packaging completed Batch Yield 95.98%	Final Filter Packaging completed Batch Yield 97.1%

The manufactured batches detailed above compare favorable to each other. Each batch was manufactured using equivalent process steps and can be deemed equivalent.

7. ANALYSIS

The Guanidine HCl 6M Solution batch that was manufactured in accordance with the current Guanidine HCl 6M Solution Batch Record DCN:20-001778 has met the BioSpectra analytical requirements associated with all Historic and Current codes. The results can be found in Table 2.

TABLE 2: ANALYSES OBSERVATIONS FOR VALIDATION BATCHES

CQA/FINISHED GOOD RELEASE SPECIFICATION		SPECIFICATION	Validation Batch 1: GH3100-026-0221-PV	Validation Batch 2: GHCL-0121-00008-PV	Validation Batch 3: GHCL-0121-00012-PV	Previously Validated Batch GH7100-012-1117-PV
Absorbance (neat)	280 nm	0.0500 a.u. max.	0.0051	0.0034	0.0065	0.0011
	260 nm	0.0500 a.u. max.	0.0246	0.0252	0.0221	0.0133
	230nm	Monitor	0.4607	0.3986	0.5625	0.4138
Appearance and Color		Clear / Colorless	Clear / Colorless	Clear / Colorless	Clear / Colorless	Clear / Colorless Liquid

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	Liquid	Liquid	Liquid	Liquid	
Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Molarity	5.8 to 6.2 M	5.8	5.9	5.9	5.95
pH (neat)	4.5 to 6.5	5.0	6.0	5.0	6.2

The manufactured batches detailed above compare favorable to each other. Each batch was manufactured using equivalent process steps and can be deemed equivalent. The results above also provide additional evidence of the equivalence between the manufacturing of the Guanidine HCl 6M solution manufactured at the Bangor, PA facility compared to those manufactured at the Stroudsburg, PA facility.

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 Guanidine HCl 6M Solution consists of an evaluation of the analyses listed in table 5. These analyses were selected based on a combination of incoming raw material specifications, finished goods requirements and known process information and the specifications were set based on this same information. Table 5 indicates which analyses are required for the Stability testing of Guanidine HCl 6M Solution at intervals 0, 3, 6, 9, 12, 18, 24, 36, 48, and 60-month intervals.

TABLE 5: STABILITY ANALYSIS

Analysis		Stability Study Requirement (Yes/No)
Absorbance (Neat)	260nm	Yes
	280nm	
Appearance and Color		Yes
Identity IR		Yes
Melamine		Yes
Molarity		Yes

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Analysis	Stability Study Requirement (Yes/No)
Solution Test	Yes

9. CONCLUSION

BioSpectra has manufactured and validated the Guanidine HCl 6M Solution to be compliant with key compliance grades up to and including the Bio Excipient grade. This Bio Excipient Grade classification requires that a product be manufactured in accordance with ICH Q7 guidelines to be suitable for use as a GMP manufactured excipient. The results obtained in this validation report deem Guanidine HCl 6M Solution manufactured using this process acceptable and equivalent to previously validated material. 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 Study for Guanidine HCl 6M Solution, GMP have provided the evidence necessary to state that the approved change from the Stroudsburg, PA facility to the Bangor, PA facility has not impacted the quality and physical characteristics of Guanidine HCl 6M Solution for Bio Excipient, Bio Pharma Grade and Bio Contract Grade Product Codes. The Guanidine HCl 6M Solution manufacturing process can be considered an approved, validated process capable of consistently producing Bio Excipient and below grade material that meets Finished Good Specifications.

All Raw Materials used for the processing of Guanidine HCl 6M Solution were approved before use in accordance with RM specifications. The Validation samples of Guanidine HCl 6M Solution will be placed into Real Time Stability and will be reported on annually. The Stability Study does not impact the current retest date or previous stability studies. All FG samples analyzed for this validation study met Finished Good Specifications.