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

BioSpectra External Validation Report

External Validation Report for the Manufacture of:

Tris Hydrochloride

To be Manufactured as the Following Codes:

THCL-32XX Bio Excipient Grade

To be Manufactured at:

BioSpectra, Inc., 1474 Rockdale Lane
Stroudsburg, Pennsylvania, 18360

In Compliance with the Standards of:

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

Manufactured to be Suitable for use as:

Pharmaceutical Excipient for Drug Manufacturing Processes

TABLE OF CONTENTS

1. INTRODUCTION:

The validation of a manufacturing process used to produce process chemicals is a requirement under IPEC-PQG Joint Good Manufacturing Practice Guide and ICH Q7 guidelines. The objective of this validation study was to assure that the manufacturing process for Tris Hydrochloride in process suite 3 at BioSpectra's Rockdale, PA facility consistently produces material that meets a set of pre-determined specifications and quality attributes as listed in Table 1. This validation study was initiated in accordance with change control SCC24-07, Additional Anhydrous Hydrogen Chloride Gas Manufacturer, which allowed for an additional manufacturer of Anhydrous Hydrogen Chloride and Tris Hydrochloride manufactured at the Bangor, PA facility to be utilized in process suite 3.

This Tris Hydrochloride validation study consisted of a concurrent validation with one validation batch to ensure that the Tris Hydrochloride manufacturing process conforms to the pre-established critical process parameters. This concurrent validation study permitted the release of the batch for commercial distribution, relying on the monitoring and analysis of the lot. The lot must conform to finished good specification before release.

2. OBJECTIVE:

The objective of this validation report is to provide a summary of the validation study for the manufacturing process for Tris Hydrochloride in process suite 3 of BioSpectra's Rockdale, PA facility. The validation batch of Tris Hydrochloride was manufactured according to the current version of the batch record. Once the manufacturing of the batch was completed, representative samples were submitted to the laboratory and 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 validation report applies to the manufacturing process for Tris Hydrochloride, Bio Excipient which includes the following process steps: Tris and Tris HCl Charged into Mother Liquor, Hydrochloric Gas Addition to Correct pH (Exothermic Reaction), 2 Step Filtration, Recrystallization, Wet Crystal Separation via Centrifuge, Fluid Bed Drying to Desired Moisture and Final Packaging.

Specifications and approval requirements for all raw materials (RM) and components have been created; therefore, these raw material and components are not covered by this report except that only approved raw material and components were used.

4. REFERENCES:

4.1. Reference Documents

4.1.1. BSI-LST-0149, Tris Hydrochloride Stability Data Card

4.1.2. MT-0001, THCl-SBG-S03-THCl-3200 / THCL-7202

4.1.3. BSI-PRL-0500, Degradation and Impurity Profile Protocol: Tris Hydrochloride S03

4.1.4. BSI-PRL-0802, Tris Hydrochloride HCl Gas Validation-S03

4.1.5. BSI-RPT-1843, Degradation and Impurity Profile Report: THCL S03 2024 Formosa Gas Validation

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

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

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

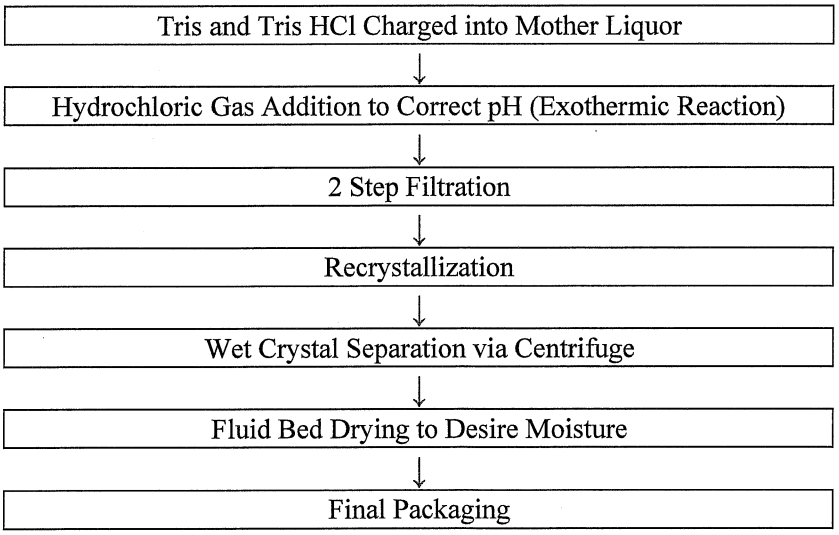
4.1.9. The Joint IPEC-PQG Good Manufacturing Practice Guide

5. EXECUTIVE SUMMARY:

The Tris Hydrochloride manufacturing process has critical process parameters (CPP's) as detailed in the Tris Hydrochloride HCl Gas Validation-S03, DCN: BSI-PRL-0500. The CPP's that were developed prior to the validation study were found to be in accordance with BioSpectra's Manufacturing Process Validation Master Plan. The utilities and processes used in the manufacturing of this product have been qualified in accordance with BioSpectra's Equipment Qualification Master Plan. The parameters for the CPP's were set for the validation batch to establish proven acceptable ranges for each CPP. The validation batch manufactured for this validation was manufactured following the current Tris Hydrochloride batch record and CPP parameter values detailed in the validation protocol. The manufacturing process for Tris Hydrochloride in process suite 3 consistently produced material that meets a set of pre-determined specifications and attributes, passing batch uniformity and finished good specification testing.

6. PROCESS FLOW DIAGRAM:

TRIS HYDROCHLORIDE PROCESS FLOW DIAGRAM



7. ANALYSIS:

The Tris Hydrochloride validation batch that was manufactured in accordance with the current Tris Hydrochloride batch record met the BioSpectra analytical requirements associated with Bio Excipient product codes THCL-32XX. The analytical results for the critical quality attributes (CQA) of the validation batch can be found in Table 1. All in-process and finished good analyses were met as required in the validation study and for finished good release.

TABLE 1: CRITICAL QUALITY ATTRIBUTES RESULTS

Composite			
CQA Analysis		**Specification**	**Lot Number**
			THCL-0224-00048-PV
Absorbance (1M)	260 nm	≤0.06 a.u.	<0.06 a.u.
	280 nm	≤0.06 a.u.	<0.06 a.u.
	400 nm	≤0.01 a.u.	<0.01 a.u.
Appearance and Color		White Crystals	White Crystals
Assay, As-Is		≥99.0%	99.5%
Assay, Dried Basis		≥99.0%	99.6%
Identification (IR)		Passes Test	Passes Test
pH (0.5M)		3.5-5.0	4.2 @ 24.8°C
Trace Metals	Arsenic (As)	≤0.0001%	<0.000045%
	Calcium (Ca)	≤0.0001%	<0.000060%
	Copper (Cu)	≤0.0001%	<0.000015%
	Iron (Fe)	≤0.0001%	<0.000030%
	Lead (Pb)	≤0.0001%	<0.000030%
	Magnesium (Mg)	≤0.0001%	<0.000060%
Melting Range		147-153°C	151-152°C
Loss on Drying (105°C)		≤0.5%	0.3%

8. ADDITIONAL INFORMATION:

8.1. Degradation and Impurity Profile

8.1.1. A degradation and impurity profile was initiated and concurrently executed for this validation in accordance with DCN: BSI-PRL-0500. The results for the degradation and impurity profile are detailed in the Degradation and Impurity Profile Report, DCN: BSI-RPT-1843.

8.2. Stability Study

8.2.1. The stability analysis for Tris Hydrochloride consists of an evaluation of the following analyses and specifications listed in Table 2 below. These analyses were selected based on a combination of the stability indication study, incoming raw material specifications, finished goods requirements and known process information and the specifications were set based on this same information. The stability study for Tris Hydrochloride consists of testing at intervals 0, 3, 6, 9, 12, 18, 24, 36, 48 and 60-month intervals.

TABLE 2: TRIS HYDROCHLORIDE STABILITY ANALYSIS (BSI-LST-0149)

ANALYSES		SPECIFICATION
Absorbance (1M)	400 nm	≤0.01 a.u.
	280 nm	≤0.06 a.u.
	260 nm	≤0.06 a.u.
Appearance and Color		White/Crystals
Assay (Dried)		≥99.0%
Identity (IR)		Passes Test
Loss on Drying @ 105°C		≤0.5%
Melting Range		147-153°C
pH (0.5M)		3.5-5.0
Water by Karl Fischer		Monitor (Target ≤0.5%)

9. CONCLUSION:

BioSpectra has successfully manufactured one validation batch of Tris Hydrochloride to be compliant with key compliance grades up to and including the Bio Excipient grade during the validation study. This Bio Excipient classification requires that a product be manufactured in accordance with ICH Q7 and IPEC guidelines and is suitable for use as a pharmaceutical excipient for drug manufacturing processes. This validation study has proven that Tris Hydrochloride manufactured utilizing the above-mentioned manufacturing process and analyzed to Bio Excipient specifications, product codes THCL-32XX, is acceptable and approved for release. The utilities and equipment used in the manufacturing process for Tris Hydrochloride have been qualified in accordance with BioSpectra's Equipment Qualification Master Plan. The results reported from the validation study have provided the evidence necessary to state that the manufacturing process for Tris Hydrochloride is in a state of control and validation. All raw materials used for the manufacturing of Tris Hydrochloride were approved before use in accordance with RM specifications. The stability samples of Tris Hydrochloride obtained during the execution of this validation study were placed on a real time stability study and will be reported annually. The stability study data will be utilized to determine the shelf life of Tris Hydrochloride manufactured by BioSpectra. All finished goods samples analyzed for this validation study met finished good specifications for THCL-32XX.