BIOSPECTRA
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BioSpectra External Validation Report

Validation Protocol for the Manufacture of:

Tris Hydrochloride, Bio Excipient

To be Manufactured as the Following Codes:

Tris Hydrochloride THCL-32XX or Below Grades

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
Guidelines for Pharmaceutical Excipients
ICH Q7 Guidance

Manufactured to be Suitable for Use as:

Pharmaceutical Excipient for Drug Manufacturing
Processes

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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 in Process Suite 3 at BioSpectra's Stroudsburg, PA facility for Tris Hydrochloride, product code THCL-3200 or below grades, is a controlled and validated process capable of consistently producing material that meets pre-established specifications and critical quality attributes. This Validation was initiated by change control BCC21-70, *Anhydrous Hydrogen Chloride Gas Manufacturer*. The current manufacturer of Anhydrous Hydrogen Chloride (AHCl), Olin Corporation, who Airgas USA LLC utilizes to fill cylinders ceased operations and will now use Niacet Corporation. The validation seeks to prove that the Anhydrous Hydrogen Chloride gas raw material manufacturer change is capable of consistently delivering quality product and remains in a validated state.

This Tris Hydrochloride Validation Study consisted of three concurrent validation batches to ensure that the Tris Hydrochloride manufacturing process conforms to the pre-established critical process parameters established using tools such as process mapping, Failure Modes Effect Analysis (FMEA) and Cause & Effect matrix, the development study, and historical manufacturing data. A Concurrent Validation is a Validation Study in which the batch can be released for commercial distribution based on the monitoring and analysis of the lot. The lot must conform to Finished Goods Specifications before release.

2. OBJECTIVE:

The objective of this Validation Report is to verify and assure that the manufacturing process for Tris Hydrochloride in Process Suite 3 of BioSpectra's Stroudsburg, PA facility consistently produces material that meets a set of pre-determined specifications as listed in Table 1 and quality attributes.

The Validation batches of Tris Hydrochloride were manufactured according to the current revision of the Batch Record. Once the manufacture of the validation 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 Tris Hydrochloride Bio Excipient Grade which includes the following process steps: charging the raw materials (including gaseous anhydrous HCl), mixing and heating, filtering, cooling to crystallize, separation and washing of the crystallized product, drying, packaging, and the testing of the finished product.

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 Tris Hydrochloride manufacturing process is a manufacturing process with Critical Process Parameters as detailed in the Validation Protocol. 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 process used in the manufacture of this product have been qualified in accordance with BioSpectra's Equipment Qualification Master Plan. The parameters for the CPP's were varied for the validation batches to establish proven acceptable ranges for each CPP. The three validation batches manufactured for this Validation were manufactured following the current Tris Hydrochloride Batch Record and CPP parameter values detailed in the Validation Protocol. The manufacturing process for Tris Hydrochloride consistently produces material that meets a set of pre-determined specifications and attributes, passing batch uniformity and Finished Good specification testing.

This Tris Hydrochloride manufacturing process in Process Suite 3 is a dedicated manufacturing process solely intended for the manufacture of Tris Hydrochloride. This manufacturing process requires 3 vessels. Vessel THPT01 serves as the charging, reaction, and heating vessel; both THSL02 and THSL03 serve as cooling and slurry vessels for centrifugation; and THML02 serves as the mother liquor (ML) storage vessel.

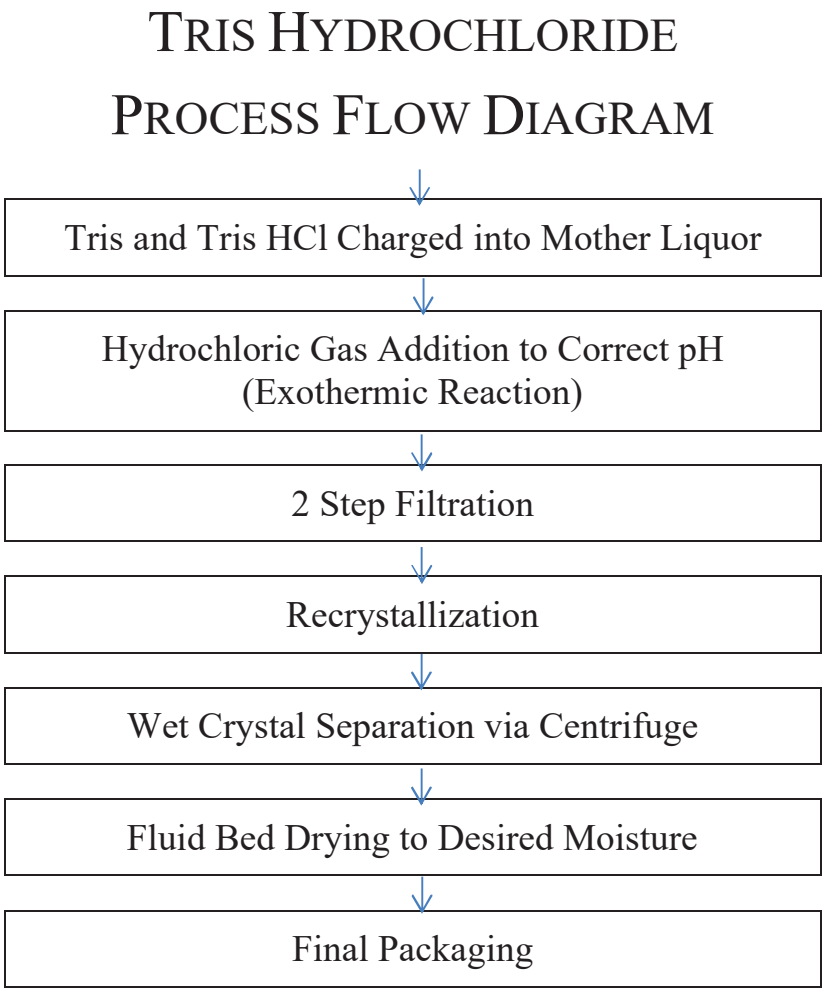
The ML is transferred to THPT01, where Tris Raw Material is added. HCl gas is then added to form Tris Hydrochloride, achieve the required pH and generate heat for dissolution. Tris HCl may be added as reprocess during this step. Once the pH is achieved, 2.0 kgs of coarse carbon is added to the process tank. This process has a two-stage filtration. The first filter is a 25-micron polypropylene bag filter and the second is a 5-micron cartridge filter. After 2.0 kgs of coarse carbon is added to the process tank, the batch is filtered to THSL02 or THSL03 through THPF03 and THPF02 where the batch is cooled to precipitate crystal.

The crystallized batch is transferred to the Centrifuge THCE01 for crystal separation. The Tris HCl Wet Crystals are washed with purified water. The ML is returned to THSL02 or THSL03 initially for batch dilution and then to THML02 or THPT01 for ML holding. The Tris HCl wet crystals (WC) are collected in gray poly lined bins for transfer to the dryer feeding system.

There are multiple centrifuge loads for each batch. The WC bins are identified during filling using product identification tags and are fed to the dryer, THFB01, in sequence through the THSC03 conveyor system. Dry material is packaged according to current order or inventory requirements as it exits the dryer.

All the equipment has been selected, designed and installed at the Stroudsburg, PA BioSpectra facility for the purposes described in this process.

5. PROCESS FLOW DIAGRAM:



6. ANALYSIS:

The Tris Hydrochloride validation batches that were manufactured in accordance with the current Tris Hydrochloride Batch Record has met the BioSpectra analytical requirements associated with product code THCL-3200 and below compliance grade. The analytical results for the critical quality attributes (CQA) of the three validation batches can be found in Table 1. All in-process and Finished Goods analyses were met as required in the Validation study and for finished good release.

TABLE 1: CRITICAL QUALITY ATTRIBUTES RESULTS FROM THE 2022 VALIDATION

CQA Analysis		CQA Specification	Validation Lots		
			THCL-0222-00054-PV	THCL-0222-00056-PV	THCL-0222-00058-PV
			Manufactured 2/28/22	Manufactured 3/4/22	Manufactured 3/8/22
Absorbance (1M)	260 nm	≤ 0.06 a.u.	0.0109 a.u.	0.0092	0.0072 a.u.
	280 nm	≤ 0.06a.u.	0.0100 a.u.	0.0080	0.0062 a.u.
	400 nm	≤ 0.01 a.u.	0.0010 a.u.	0.0013	0.0006 a.u.
Appearance and Color		White/Crystals	White/Crystals	White/Crystals	White/Crystals
Assay, As-Is		99.0% minimum	99.50%	99.69%	99.87%
Assay, Dried-Basis		99.0% minimum	99.66%	99.78%	99.85%
Identification (IR)		Passes Test	Passes Test	Passes Test	Passes Test
pH (0.5M)		3.5-5.0	4.35 @ 25.3°C	4.34 @ 25.0 ºC	4.17 @ 26.8°C
Arsenic (As)		1 ppm max.	<0.45 ppm	<0.45 ppm	<0.45 ppm
Calcium (Ca)		1 ppm max.	<0.60 ppm	<0.60 ppm	<0.60 ppm
Copper (Cu)		1 ppm max.	<0.15 ppm	<0.15 ppm	<0.15 ppm
Iron (Fe)		1 ppm max.	<0.30 ppm	<0.30 ppm	<0.30 ppm
Lead (Pb)		1 ppm max.	<0.30 ppm	<0.30 ppm	<0.30 ppm
Magnesium (Mg)		1 ppm max.	<0.60 ppm	<0.60 ppm	<0.60 ppm
Melting Range		147 - 153ºC	150.1 – 151.3°C	150.3 – 151.3 ºC	150.5 – 151.5°C
Loss on Drying (105°C)		0.5% max.	0.1288%	0.2189%	0.0546%

7. ADDITIONAL INFORMATION:

7.1. Degradation and Impurity Profile

7.1.1. A Degradation and Impurity profile was performed for this validation in accordance with Degradation and Impurity Profile Protocol: Tris Hydrochloride 2022 DCN: BSI-PRL-0500. The Degradation and Impurity Profile will be reported on in the Degradation and Impurity Profile Report.

7.2. Stability Study

7.2.1. The Stability Analysis for Tris Hydrochloride consists of an evaluation of the following analyses and associated specifications detailed in Table 2. 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. 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 intervals.

TABLE 2: STABILITY ANALYSIS

ANALYSES	SPECIFICATION	
Absorbance (1M)	TH7201, TH3203	0.01 max @ 400 nm 0.06 max @ 280 nm 0.06 max @ 260 nm
	TH7202	0.02 max @ 280 nm 0.02 max @ 260 nm
Appearance and Color	TH7201, TH3203	White/Crystals
Assay	TH7201	99.0-103.0%
	TH7202	99.0% min
	TH3203	99.5% min
Identity (IR)	Passes Test	
Loss on Drying	TH7201, TH3203	0.5% max @ 105°C
	TH7202	0.4% max @ 110°C
Melting Range	TH7201	147 – 153°C
	TH7202	Not Applicable
	TH3203	150 – 153°C
pH	TH7201 (0.5M)	3.5 – 5.0
	TH7202 (1.0M)	3.7 – 4.7
	TH3203 (0.5M)	4.0 – 5.0

8. CONCLUSION:

BioSpectra has successfully manufactured three batches of validated Bio Excipient Grade Tris Hydrochloride 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 IPEC and ICH Q7 guidelines and is suitable for use as an excipient. The results obtained in this validation report deem Tris Hydrochloride manufactured using this process acceptable. 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 Tris Hydrochloride have provided the evidence necessary to state that the approved Anhydrous Hydrogen Chloride (AHCl) gas change from Olin Corporation to Niacet Corporation have not impacted the quality and physical characteristics of Tris Hydrochloride for product codes THCL-3200 and below compliance grades. All Raw Materials used for the processing of Tris Hydrochloride were approved before use in accordance with RM specifications. The Validation samples of Tris Hydrochloride 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 finished good samples analyzed for all three batches of this validation study met Finished Good Specifications for product code THCL-3200 or below compliance grades.