BIOSPECTRA
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BioSpectra External Validation Report

Validation Protocol for the Manufacture of:

Tris Continuous, Bio Excipient

To be Manufactured as the Following Codes:

TRIS-3200 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
Guide for Bio Excipients
ICH Q7 Guidance

Manufactured to be Suitable for Use as:

Excipient for Drug Manufacturing

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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 Manufacturing Suite 4 at BioSpectra's Stroudsburg, PA facility for Tris Bio Excipient grade, product code TRIS-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 controls SCC21-11, a change control approved to manufacture Tris Bio Excipient in Manufacturing Suite 4 in addition to the currently validated Manufacturing Suite 1 and SCC21-03, a change control approved to manufacture Tris Bio Excipient with a new Tris raw material supplier. The validation seeks to prove the manufacturing suite change is capable of consistently delivering quality product and remains in a validated state.

This Tris Continuous Bio Excipient grade validation study consisted of three concurrent validation batches to ensure that the Tris Continuous Bio Excipient grade 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 Continuous Bio Excipient grade in Manufacturing Suite 4 of BioSpectra's Stroudsburg, PA facility consistently produces material that meets a set of pre-determined specifications as listed in Table 1: Critical Quality Attributes.

The validation batches of Tris Continuous Bio Excipient grade were manufactured according to the current revision of the batch record. Once the manufacture of each validation batch 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 Continuous Bio Excipient grade, which includes the following process steps: charging Tris raw material to heated mother liquor, 4 step purification, cooling to crystallize, wet crystal separation via centrifugation, drying through fluid bed dryers until desired moisture is reached and final packaging of the 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. REFERENCES:

4.1. Reference Documents

4.1.1. BSI-LST-0158, Tris Bio Excipient Stability Data Card

4.1.2. BSI-MPR-0056, Tris Continuous Bio Excipient Batch Record – S04

4.1.3. BSI-PRL-0463, Tris Continuous Stroudsburg S04, Process Validation Protocol

4.1.4. BSI-PRL-0512, Degradation and Impurity Protocol: Tris Continuous 2022

4.1.5. BSI-RPT-1070, Degradation and Impurity Profile Report: Tris 2022-S04

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

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

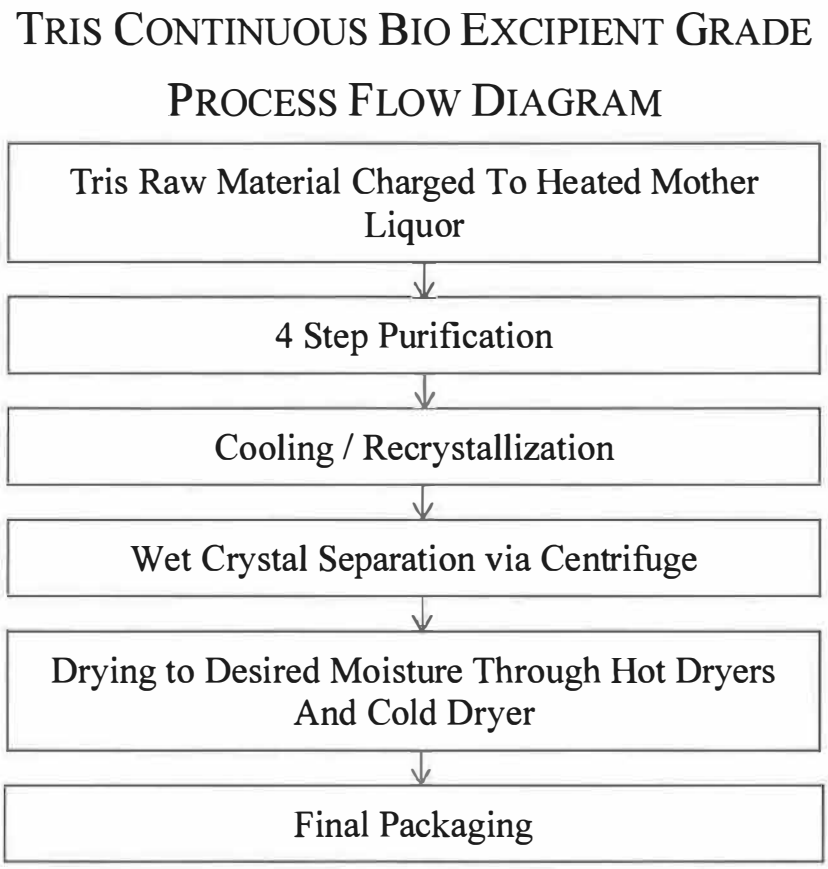
4.1.8. ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

4.1.9. The Joint IPEC-PQG Good Manufacturing Practice Guide

5. EXECUTIVE SUMMARY:

The Tris Continuous Bio Excipient grade 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 validation batches manufactured for this validation were manufactured following the current Tris Continuous Bio Excipient Grade Batch Record and CPP parameter values detailed in the validation protocol. The manufacturing process for Tris Continuous Bio Excipient Grade consistently produces material that meets a set of pre-determined specifications and attributes, passing batch uniformity and finished good specification testing.

6. PROCESS FLOW DIAGRAM:



7. ANALYSIS:

The Tris Continuous Bio Excipient Grade validation batches that were manufactured in accordance with the current Tris Continuous Bio Excipient Grade Batch Record have met the BioSpectra analytical requirements associated with product code TRIS-3200 and below compliance grades. The analytical results for the critical quality attributes (CQA) of the validation batch 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 PROCESS VALIDATION

Composite					
CQA Analysis		**Specification**	**Lot Number**		
			TRIS-0222-00036-PV	**TRIS-0222-00037-PV**	**TRIS-0222-00038-PV**
Absorbance (1M)	**260nm**	**≤ 0.06 a.u.**	0.01 a.u.	0.01 a.u.	0.01 a.u.
	280nm	**≤ 0.06 a.u.**	<0.06 a.u.	0.01 a.u.	0.01 a.u.
	400nm	**≤ 0.01 a.u.**	<0.01 a.u.	<0.01 a.u.	<0.01 a.u.
Appearance and Color		**White Crystals**	White/Crystals	White/Crystals	White/Crystals
Assay (Ultrapure)		**≥ 99.9%**	100.5%	100.2%	100.2%
Assay (USP)		**99.0-101.0%**	100.3%	99.6%	99.8%
pH (5% Solution)		**10.0-11.5**	10.7 @ 24.6°C	10.9 @ 25.7°C	10.7 @ 23.7°C
Insoluble Matter		**0.005% max.**	<0.005%	<0.001%	<0.001%
Melting Range		**168-172°C**	171 – 172°C	171 – 172°C	171 – 172°C
Loss on Drying		**0.5% max.**	0.2%	0.2%	0.1%

8. ADDITIONAL INFORMATION:

8.1. Degradation and Impurity Profile

8.1.1. A degradation and impurity profile was performed for this validation in accordance with the Degradation and Impurity Profile Protocol: Tris Continuous 2022, DCN: BSI-PRL-0512. The degradation and impurity profile testing results were detailed in the Degradation and Impurity Profile Report: Tris 2022 – S04, DCN: BSI-RPT-1070.

8.2. Stability Study

8.2.1. The stability analysis for Tris Bio Excipient Grade 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 real time stability program undergoes stability analysis at 0, 3, 6, 9, 12, 18, 24, 36, 48 and 60-month intervals.

TABLE 2: STABILITY ANALYSIS

ANALYSES	SPECIFICATION
Absorbance (1M)	0.01 a.u. max @ 400 nm
	0.06 a.u. max @ 280 nm
	0.06 a.u. max @ 260 nm
Appearance and Color	White / Crystals
Assay	99.0 – 101.0%
Identification (UATR)	Passes Test
Loss on Drying	0.5% max
Melting Range	168-172 °C

9. CONCLUSION:

BioSpectra has successfully manufactured three batches of Tris Continuous Bio Excipient Grade material 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 Continuous Bio Excipient Grade 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 Bio Excipient Grade have provided the evidence necessary to state that the approved changes to manufacture Tris Bio Excipient using a new Tris Raw material supplier and in Manufacturing Suite 4 have not impacted the quality and physical characteristics of Tris Continuous Bio Excipient Grade for product codes TRIS-3200 and below compliance grades. All raw materials used for the processing of Tris Continuous Bio Excipient Grade were approved before use in accordance with raw material specifications. The validation samples of Tris Continuous Bio Excipient Grade were placed on to 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 this validation study met finished good specifications for product code TRIS-3200 or below compliance grades.