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

BioSpectra Validation External Report

Validation Report for the Manufacture of:

Trehalose, Dihydrate

To be Manufactured as the Following Codes:

TRED-32XX or Below Compliance 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:

An 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 external validation report describes the process as performed using, Process Suite N02 located in Zone N of 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 Trehalose, Dihydrate Validation Study was a concurrent validation to ensure that the Trehalose, Dihydrate process conforms to the pre-established critical process parameters as described in the validation protocol. 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 Trehalose, Dihydrate to be manufactured.

2. OBJECTIVE:

The objective of this External Validation Report is to verify and assure that the manufacturing process for Trehalose, Dihydrate consistently produces material that meets a set of pre-determined specifications as listed in Table 2. This validation was performed due to utilizing a new raw material supply chain and initiated by Bangor Change Control BCC21-13 Trehalose Raw Material Supply Chain.

This validation included three batches of Trehalose, Dihydrate, 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 the manufacturing process of Trehalose, Dihydrate, Bio Excipient Grade, within this validation study. This manufacturing process includes the following process steps: charging the raw materials, mixing and heating, filtering, cooling to crystallize, separating the wet crystals, washing of the crystallized product, drying, packaging, and 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.

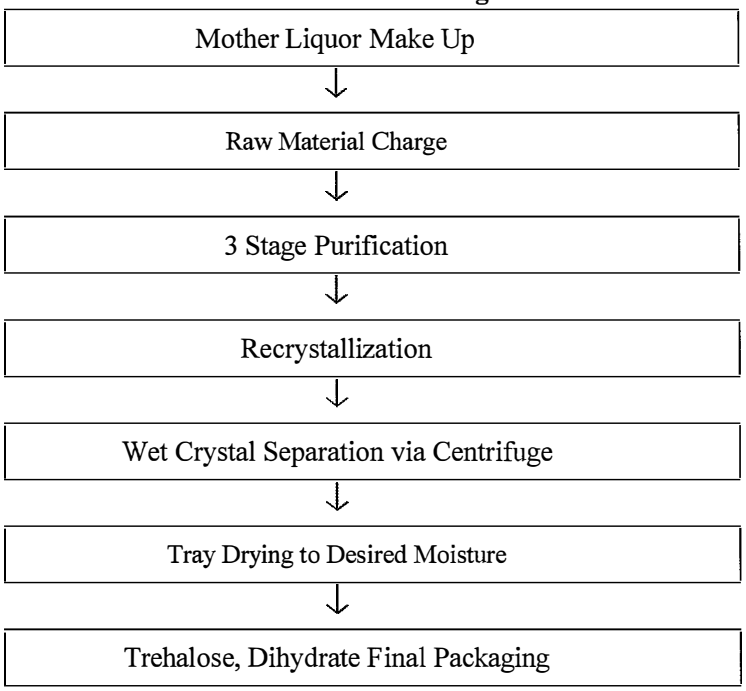
4. EXECUTIVE SUMMARY:

The Validation Study for Trehalose, Dihydrate was performed due to change control referenced as BCC21-13. This change was approved for the utilization of a new raw material supply chain. Because the change control pertains to just the supply chain, the process steps are unaffected by this change control. This information is detailed in the supplied change notification and approved change control form.

The Trehalose, Dihydrate 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 equipment used in the manufacture of this product have been qualified in accordance with BioSpectra's Equipment Qualification Master Plan. The manufacturing for all three batches manufactured for this validation study were deemed successful and these batches will be released in accordance with the Validation plan and the approval of all related manufacturing and QC documentation.

5. PROCESS FLOW DIAGRAM:

Trehalose Process Flow Diagram



6. MANUFACTURING OBSERVATIONS:

The three Trehalose, Dihydrate batches that were manufactured in accordance with the current Trehalose, Dihydrate Bio Excipient Grade Batch Record DCN:BSI-MPR-0024 v.3.0 and have met the requirements. The manufacturing observations for the three Trehalose, Dihydrate batches manufactured and used for this validation study of material lot numbers, TRED-0121-00002-PV, TRED-0121-00003-PV and TRED-0121-00004-PV met the pre-established validation parameters.

7. ANALYSIS:

The Trehalose Dihydrate batches that were manufactured in accordance with the current Trehalose Dihydrate Bio Excipient Grade Batch Record, DCN:BSI-MPR-0024 v.3.0 was analyzed in accordance with approved Trehalose Testing Methods, DCN:BSI-ATM-0027 and has met the BioSpectra analytical requirements associated with Product Code:TRED-3250. The results can be found in Table 3.

Table 1: CQA Analytical Results for Trehalose, Dihydrate Validation Batches

Method		Specification	Validation Batch 1: TRED-0121-00002-PV	Validation Batch 2: TRED-0121-00003-PV	Validation Batch 3: TRED-0121-00004-PV
Appearance and Color		White to Off-White Crystalline powder	White Crystalline powder	White Crystalline powder	White Crystalline powder
Assay		98.0% to 101.0%	99.6%	100.3%	100.8%
Color and Clarity of Solution		A720nm: ≤ 0.050 a.u. A420nm – A720nm: ≤0.100 a.u.	A720 nm: 0.001 A420nm-A720nm: 0.021	A720 nm: 0.002 A420nm-A720nm: 0.014	A720 nm: <0.003 A420nm-A720nm: 0.014
Residual Isopropyl Alcohol		≤ 5000 ppm	<5000 ppm	<5000 ppm	<5000 ppm
Identification A		Passes Test	Passes Test	Passes Test	Passes Test
Identification B		Passes Test	Passes Test	Passes Test	Passes Test
Identification C		Passes Test	Passes Test	Passes Test	Passes Test
Endotoxins		≤ 2.4 EU/g	<2.4 EU/g	<2.4 EU/g	<2.4 EU/g
Microbial Content	Escherichia coli	Absent/g	Absent	Absent	Absent
	Salmonella species	Absent/10g	Absent	Absent	Absent
	TAMC	≤ 100 CFU/g	<10 CFU/g	<10 CFU/g	<10 CFU/g
	TYMC	≤ 100 CFU/g	<10 CFU/g	<10 CFU/g	<10 CFU/g
Water (Karl Fischer)		9.0 to 11.0%	9.8%	9.5%	9.4%

8. ADDITIONAL INFORMATION:

8.1. Degradation and Impurity Profile

8.1.1. A Degradation and Impurity profile is performed for this validation. The degradation and impurity profile was completed for this validation study. Refer to BSI-RPT-0798.

8.2. Stability Study

8.2.1. The Stability Analysis for Trehalose, Dihydrate consists of an evaluation of the analyses detailed in Table 3. These analyses were selected based on a combination finished goods requirements and Stability Indicating Protocol. The analyses listed below will be performed for each validation batch and 1 batch per year manufactured. Each batch placed on the Long-Term Stability Program will undergo stability analysis at intervals 0, 3, 6, 9, 12, 18, 24, and 36-month.

Table 2: Stability Analysis

Analysis		Stability Specification
Appearance		White to Off White Crystalline Powder
Assay		98.0-101.0%
Color and Clarity of Solution		A720 ≤0.050 and A420-A720 ≤0.100
Dextrins, Soluble Starch and Sulfite		Passes Test
Identification Test A (UATR)		Conforms to Standard
Impurities	Maltotriose (Impurity B)	≤0.5%
	Total Impurities with RRT <1.0	≤0.5%
	Total Impurities with RRT >1.0	≤0.5%
	Glucose (Impurity A)	≤0.5%
	Any other Impurities	≤0.2%
	Sum of Gluose, Maltotriose and Other Impurity	≤1.0%
pH @ 25 °C		4.5 - 6.5
Specific Rotation/Optical Rotation		+197° to +201° @ 20°C
Water (Karl Fisher)		9.0 - 11.0%

9. CONCLUSION:

BioSpectra has manufactured and validated the Trehalose, Dihydrate manufacturing process, Product Code: TRED-3250 to be compliant with key compliance grades up to and including the Bio Excipient grade. This Bio Excipient Grade classification requires that the excipient be manufactured in accordance with ICH Q7 Good Manufacturing Practice Guide to be suitable for use as a GMP manufactured Excipient. The results obtained during this validation study and subsequent analysis provide evidence that the Trehalose, Dihydrate manufactured using approved process will consistently meet the approved specifications for product code TRED-3250. 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 three batches of Trehalose, Dihydrate for this Validation Study provided the evidence necessary to confirm that the approved change for utilization of the new raw material supply chain has not impacted the quality and physical characteristics of Trehalose, Dihydrate. The Trehalose Dihydrate manufacturing process, using Process Suite N02, can be considered an approved, validated process capable of consistently producing Bio Excipient Grade material that meets Finished Good Specifications, TRED-3250. Validation samples of Trehalose Dihydrate will be placed into Long Time Stability and will be reported on annually. The Stability Study does not impact the current retest date or previous stability studies.