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

BioSpectra External Validation Report

Validation Protocol for the Manufacture of:

Dextran Sulfate 8000

To be Manufactured as the Following Codes:

Dextran Sulfate 8000
DXSE-32XX Bio Excipient and Below Compliance Grades

To be Manufactured at:

BioSpectra, Inc., 100 Majestic Way, Bangor Pennsylvania, 18013

In Compliance with the Standards of:

The Joint IPEC – PQG Good Manufacturing Practice Guide
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 IPEC-PQG Joint Good Manufacturing Practice Guide and ICH Q7 Good Manufacturing Practice guidelines. The objective of this validation study was to assure that the manufacturing process for Dextran Sulfate 8000 in Process Room G13 at BioSpectra's Bangor, PA facility analyzed to product code DXSE-4250 is a controlled and validated process capable of consistently producing material that meets pre-established specifications and critical quality attributes. This validation study was initiated due to Dextran Sulfate 8000 being a newly developed manufacturing process. The validation seeks to prove that the Dextran Sulfate 8000 manufacturing process is capable of consistently delivering quality product.

This Dextran Sulfate 8000 Validation Study consisted of a prospective validation with three validation batches to ensure that the Dextran Sulfate 8000 manufacturing process conforms to the pre-established critical process parameters. This prospective validation study required that the validation of this process is completed before the commercial distribution of Finished Good Dextran Sulfate 8000 with the expected intended use.

2. OBJECTIVE:

The objective of this External Validation Report is to provide a summary of the Validation Study for the manufacturing process for Dextran Sulfate 8000 in Process Room G13 of BioSpectra's Bangor, PA facility. The Dextran Sulfate 8000 Validation Study was performed to verify and assure that the manufacturing process for Dextran Sulfate 8000 consistently produces material that meets a set of pre-determined quality attribute specifications as listed in Table 1. This is the first Validation study intended to validate the Dextran Sulfate 8000 manufacturing process.

The Validation batches of Dextran Sulfate 8000 were manufactured according to the current version of the Batch Record. Once the manufacturing of the batches were completed, representative samples were submitted to the QC 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 External Validation Report applies to the manufacturing process for Dextran Sulfate 8000, Bio Excipient Grade which includes the following process steps: batch raw material charge, purification, spray drying, manual blend and 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. REFERENCES:

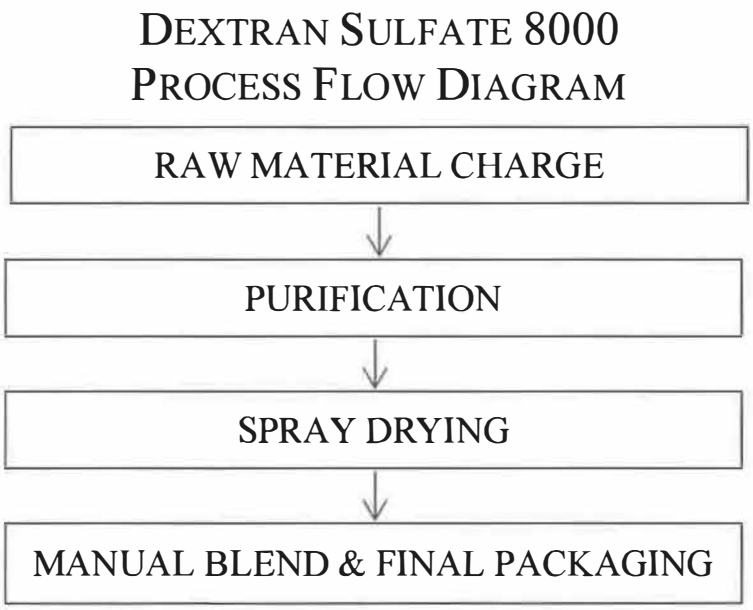
4.1. Reference Documents

4.1.1. BSI-LST-0248, Dextran Sulfate 8000 Stability Data Card
4.1.2. BSI-PRL-0681, Dextran Sulfate 8000 Bio Excipient Grade Validation Protocol
4.1.3. BSI-PRL-0685, Degradation and Impurity Profile Protocol: Dextran Sulfate 8000
4.1.4. BSI-PRL-0692, Dextran Sulfate 8000 Bio Excipient Grade Validation Protocol Addendum
4.1.5. BSI-SOP-0292, Manufacturing Process Validation Master Plan
4.1.6. BSI-SOP-0435, Equipment Qualification Master Plan
4.1.7. ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
4.1.8. The Joint IPEC-PQG Good Manufacturing Practice Guide

5. EXECUTIVE SUMMARY:

The Dextran Sulfate 8000 manufacturing process is a manufacturing process with Critical Process Parameters (CPP's) as detailed in the Validation Protocol, BSI-PRL-0692. 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 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 Dextran Sulfate 8000 Batch Record and CPP parameter values detailed in the Validation Protocol. The manufacturing process for Dextran Sulfate 8000 utilizing Process Room G13 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:



7. ANALYSIS:

The Dextran Sulfate 8000 batches that were manufactured in accordance with the current Dextran Sulfate 8000 Bio Excipient Grade Batch Record have met the BioSpectra analytical requirements associated with product code DXSE-4250. 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

Required Analysis	Specification	Lot Numbers		
		DXSE-0123-00004-PV	DXSE-0123-00006-PV	DXSE-0123-00007-PV
Appearance and Color	Off-White to Light Yellow Powder	Off White to Light Yellow Powder	Off White to Light Yellow Powder	Off White to Light Yellow Powder
Clarity (20% Solution) Abs @ 360nm	≤0.9 OD Unit	0.1 OD Unit	0.1 OD Unit	0.1 OD Unit
Glucose Content	35 – 48%	37%	37%	36%
Loss on Drying	≤10%	7%	8%	6%
Total Bioburden	≤100 CFU/g	<10 CFU/g	<10 CFU/g	20 CFU/g

8. ADDITIONAL INFORMATION:

8.1. Degradation and Impurity Profile

8.1.1. A Degradation and Impurity profile was initiated and completed for this validation in accordance with DCN: BSI-PRL-0685. Results will be documented in the Degradation and Impurity Profile Report.

8.2. Stability Study

8.2.1. The Stability Analysis for Dextran Sulfate 8000 consists of an evaluation of the following analyses, and specifications listed in Table 2 below. The Stability Study for Dextran Sulfate 8000 consists of testing at intervals 0, 3, 6, 9, 12, 18, 24, 36, 48, and 60 month intervals. 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.

TABLE 2: Dextran Sulfate 8000 Stability Analysis

ANALYSES	SPECIFICATION
Appearance	Off white to light yellow powder
Clarity (20% solution) Absorbance at 360 nm	≤0.9 OD unit
Endotoxin	≤0.012 EU/mg
Identification (Colorimetric)	Passes Test
Loss on Drying	≤ 10%
pH (1% solution)	5.0 to 7.5
Total Bioburden	≤100 CFU/g

9. CONCLUSION:

BioSpectra has successfully manufactured three batches of Dextran Sulfate 8000, Bio Excipient Grade, to be compliant with key compliance grades up to and including the Bio Excipient Grade during the Validation Study. This Bio Excipient Grade classification requires that a product be manufactured in accordance with ICH Q7 and IPEC guidelines and is suitable for use as an excipient. This validation study has proven that Dextran Sulfate 8000 manufactured utilizing the above-mentioned manufacturing process and analyzed to Product Code DXSE-4250 is acceptable and meets finished goods specifications. The utilities and equipment used in the manufacturing process for Dextran Sulfate 8000 have been qualified in accordance with BioSpectra's Equipment Qualification Master Plan. The results reported from the Validation Study for Dextran Sulfate 8000 have provided the evidence necessary to state that the new manufacturing process for Dextran Sulfate 8000, analyzed to Product Code DXSE-4250 is in a state of control and validation.

All Raw Materials used for the processing of Dextran Sulfate 8000 were approved before use in accordance with RM specifications. The Stability Samples of Dextran Sulfate 8000 obtained during the execution of this Validation study will be placed on a Real Time Stability Study and will be reported on annually. The Stability Study data will be utilized to support the shelf life, of Dextran Sulfate 8000 manufactured by BioSpectra, provided based on industry standard.