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DEGRADATION AND IMPURITY PROFILE REPORT: DEXTRAN SODIUM SULFATE 8000

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1. PURPOSE AND SCOPE:

1.1. The impurity profiling of Dextran Sodium Sulfate 8000 was intended to identify and potentially quantify impurities found in Dextran Sodium Sulfate 8000 (CAS 9011-18-1) product manufactured and purified at BioSpectra.

1.1.1. In the case where an impurity was found, a limit was set to the maximum allowable without measurable compromise to predetermined critical quality attributes or toxicity. In the case where a limit could not be set, a procedure was written and followed, to identify if the possible impurity was present or not (i.e. an identity test, which is qualitative and not quantitative).

1.1.2. The profiling results and data allowed BioSpectra to understand the purity and characteristics of Dextran Sodium Sulfate 8000 through all stages of manufacturing.

1.1.3. The four stages of Dextran Sodium Sulfate 8000 that were tested are Raw Material solution pre-filtration, Post-Purification Solution, 1st 10-gallon FG Spray Dried Increment Sample, and Finished Good Composite Sample.

1.1.3.1. If adjustment was required, the pre-filtration sample to be tested was the sample after adjustment.

1.1.4. Tables were generated to include all sample results in the Dextran Sodium Sulfate 8000 Degradation and Impurity Profile Report.

1.1.5. The tests that were used to determine the presence of impurities and degradation products were as follows:

1.1.5.1. Appearance and Color

1.1.5.1.1. All four stages.

1.1.5.2. Total Bioburden (reported from TAMC result)

1.1.5.2.1. All four stages.

1.1.5.2.2. All individual Samples for Total Bioburden except for the Composite sample will be submitted in accordance with Process Validation Protocol.

1.1.5.3. Chloride Content

1.1.5.3.1. All four stages.

1.1.5.4. Clarity (20% Solution) at 360nm

1.1.5.4.1. All four stages.

1.1.5.5. Elemental Impurities

1.1.5.5.1. All four stages.

1.1.5.6. Endotoxin

1.1.5.6.1. All four stages

1.1.5.7. Free Sulfate

1.1.5.7.1. All four stages.

1.1.5.8. Glucose Content

1.1.5.8.1. All four stages.

1.1.5.9. Identification(s)

1.1.5.9.1. All four stages.

1.1.5.10. Iron:

1.1.5.10.1. All four stages.

1.1.5.11. Loss on Drying

1.1.5.11.1. All four stages.

1.1.5.12. Manganese

1.1.5.12.1. All four stages.

1.1.5.13. pH (1% Solution)

1.1.5.13.1. All four stages.

1.1.5.14. Residue on Ignition
1.1.5.14.1. All four stages.
1.1.5.15. Pyridine
1.1.5.15.1. All four stages.
1.1.5.16. Residual Solvents (Methanol and Isopropyl Alcohol)
1.1.5.16.1. All four stages.

1.2. All results were recorded in the appropriate laboratory documentation. The results were detailed and analyzed in the degradation and impurity profile report. This report includes all relevant data as well as references to the initial documented results. This report discusses any impurities found in the product and includes a specification for any limits on the impurities found when applicable.

2. RESPONSIBILITIES:

2.1. The Associate Director of Product Life Cycle was responsible for control, implementation, training,and maintenance of this report.
2.2. The Laboratory Analysts (or qualified designees) were responsible for performing the testing stated in the protocol and recording all results.
2.3. It was the responsibility of all personnel to read and understand the SDS and don the appropriate PPE for handling and disposing of chemicals in a safe manner.

3. REFERENCES:

3.1. BSI-ATM-0091, Dextran Sulfate 8000 MW (DS8) Testing Methods
3.2. BSI-ATM-0093 Analytical Method for the Determination of ICH Q3D Elemental Impurities (Class 1, 2A, 2B, 3, & 4) by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) in Dextran Sulfate
3.3. BSI-ATM-0100, Analytical Method for the Determination of Manganese by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) in Dextran Sulfate
3.4. BSI-ATM-0106, Dextran Sulfate Solution Testing Methods
3.5. BSI-MEM-0130, Endosafe NexGen PTS Endotoxin Reader: Qualified Products
3.6. BSI-RPT-1296, Analytical Method Validation Report: Dextran Sulfate Glucose Content via UV/Vis Spectroscopy
3.7. BSI-PRL-0685, Degradation and Impurity Protocol: Dextran Sulfate 8000
3.8. BSI-PRL-0692, Dextran Sulfate 8000 Bio Excipient Grade Validation Protocol Addendum
3.9. BSI-RPT-1339, Analytical Method Validation report: Limit of Pyridine in Dextran Sulfate
3.10. BSI-RPT-1438, Elemental Impurity Assessment: Dextran Sulfate 8000, G13 2023
3.11. BSI-SOP-0069, Preparation of Samples for Outside Testing
3.12. BSI-SOP-0090, Lambda 25 UV/Vis Operation and Calibration
3.13. BSI-SOP-0094, Muffle Furnace SOP and Calibration
3.14. BSI-SOP-0098, Balance SOP
3.15. BSI-SOP-0102, Degradation and Impurity Profiling SOP
3.16. BSI-SOP-0126, Laboratory Notebooks
3.17. BSI-SOP-0134, Pipette SOP
3.18. BSI-SOP-0244, VWR Gravity Convection Oven Operation and Calibration (Model Number 414005-106)
3.19. BSI-SOP-0255, XL200 pH/mV/Conductivity Meter SOP
3.20. BSI-SOP-0303, NexION 350X ICP-MS SOP
3.21. BSI-SOP-0316, Shimadzu QP2010S GC/MS SOP
3.22. BSI-SOP-0345, Endosafe Nexgen-PTS Endotoxin Reader SOP.

4. EQUIPMENT:

4.1. Analytical Balance
4.2. Blue M Convection Oven

4.3. Bunsen Burner
4.4. Calibrated Pipette
4.5. Calibrated Timer
4.6. Endosafe NexGen PTS Endotoxin Reader
4.7. Hot Plate
4.8. Lambda 25 UV/Vis Spectrophotometer
4.9. Litmus Paper
4.10. Metrohm 914 pH Conductometer
4.11. Muffle Furnace
4.12. Perkin Elmer NexION 350X ICP-MS
4.13. pH Probe
4.14. Shimadzu QP2010S GC/MS
4.15. VWR Gravity Convection Oven
4.16. XL200 pH/mV/Conductivity Meter

5. RESULTS:

5.1. APPEARANCE AND COLOR:

5.1.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Appearance and Color testing are detailed in the table below.

TABLE 1: APPEARANCE AND COLOR

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor	Clear, Colorless Liquid
DXSE-0123-00006-PV Pre-Filtration			Clear, Yellow Liquid
DXSE-0123-00007-PV Pre-Filtration			Clear, Yellow Liquid
DXSE-0123-00004-PV Post Filtration	Post Filtration		Clear, Colorless Liquid
DXSE-0123-00006-PV Post Filtration			Clear, Slightly Yellow Liquid
DXSE-0123-00007-PV Post Filtration			Clear, Slightly Yellow Liquid
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	Off White to Light Yellow Powder	Off White to Light Yellow Powder
DXSE-0123-00006-PV Increment 1			Off-White to Light Yellow Powder
DXSE-0123-00007-PV Increment 1			Off White to Light Yellow Powder
DXSE-0123-00004-PV	Finished Good		Off White to Light Yellow Powder
DXSE-0123-00006-PV			Off White to Light Yellow Powder
DXSE-0123-00007-PV			Off White to Light Yellow Powder

5.2. TOTAL BIOBURDEN :

5.2.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Total Bioburden testing are detailed in the table below.

TABLE 2: TOTAL BIOBURDEN

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor	<100 CFU/g
DXSE-0123-00006-PV Pre-Filtration			<100 CFU/g
DXSE-0123-00007-PV Pre-Filtration			<100 CFU/g
DXSE-0123-00004-PV Post Filtration	Post Filtration		<100 CFU/g
DXSE-0123-00006-PV Post Filtration			<100 CFU/g
DXSE-0123-00007-PV Post Filtration			<100 CFU/g
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	≤100 CFU/g	<10 CFU/g
DXSE-0123-00006-PV Increment 1			<10 CFU/g
DXSE-0123-00007-PV Increment 1			<10 CFU/g
DXSE-0123-00004-PV	Finished Good		<10 CFU/g
DXSE-0123-00006-PV			<10 CFU/g
DXSE-0123-00007-PV			20 CFU/g

5.3. CHLORIDE CONTENT :

5.3.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Chloride content testing are detailed in the table below.

TABLE 3: CHLORIDE CONTENT

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor	<1000 ppm
DXSE-0123-00006-PV Pre-Filtration			<1000 ppm
DXSE-0123-00007-PV Pre-Filtration			<1000 ppm
DXSE-0123-00004-PV Post Filtration	Post Filtration		<1000 ppm
DXSE-0123-00006-PV Post Filtration			<1000 ppm
DXSE-0123-00007-PV Post Filtration			<1000 ppm
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	≤1000ppm	<1000 ppm
DXSE-0123-00006-PV Increment 1			<1000 ppm
DXSE-0123-00007-PV Increment 1			<1000 ppm
DXSE-0123-00004-PV	Finished Good		<1000 ppm
DXSE-0123-00006-PV			<1000 ppm
DXSE-0123-00007-PV			<1000 ppm

5.4. CLARITY (20% SOLUTION AT 360nm) :

5.4.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Clarity (20% Solution) testing are detailed in the table below.

TABLE 4: CLARITY (20% SOLUTION)

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor	0.1002 OD Unit
DXSE-0123-00006-PV Pre-Filtration			0.1971 OD Unit
DXSE-0123-00007-PV Pre-Filtration			0.1608 OD Unit
DXSE-0123-00004-PV Post Filtration	Post Filtration		0.0365 OD Unit
DXSE-0123-00006-PV Post Filtration			0.0820 OD Unit
DXSE-0123-00007-PV Post Filtration			0.0868 OD Unit
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	0.9 OD Unit Max	0.1 OD Unit
DXSE-0123-00006-PV Increment 1			0.1 OD Unit
DXSE-0123-00007-PV Increment 1			0.1 OD Unit
DXSE-0123-00004-PV	Finished Good		0.1 OD Unit
DXSE-0123-00006-PV			0.1 OD Unit
DXSE-0123-00007-PV			0.1 OD Unit

5.5. ELEMENTAL IMPURITIES :

5.5.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Elemental Impurities testing are detailed in the table below.

TABLE 5: ELEMENTAL IMPURITIES

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor	Refer to BSI-RPT-1438 for Elemental Impurity Assessment
DXSE-0123-00006-PV Pre-Filtration			
DXSE-0123-00007-PV Pre-Filtration			
DXSE-0123-00004-PV Post Filtration	Post Filtration		
DXSE-0123-00006-PV Post Filtration			
DXSE-0123-00007-PV Post Filtration			
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	Complies with USP <232><233>	
DXSE-0123-00006-PV Increment 1			
DXSE-0123-00007-PV Increment 1			
DXSE-0123-00004-PV	Finished Good		
DXSE-0123-00006-PV			
DXSE-0123-00007-PV			

5.6. ENDOTOXIN :

5.6.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Endotoxin testing are detailed in the table below.

TABLE 6: ENDOTOXIN

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor	<0.0050 EU/mg
DXSE-0123-00006-PV Pre-Filtration			<0.0050 EU/mg
DXSE-0123-00007-PV Pre-Filtration			<0.0050 EU/mg
DXSE-0123-00004-PV Post Filtration	Post Filtration		<0.0050 EU/mg
DXSE-0123-00006-PV Post Filtration			<0.0050 EU/mg
DXSE-0123-00007-PV Post Filtration			<0.0050 EU/mg
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	≤0.012 EU/mg	<0.005 EU/mg
DXSE-0123-00006-PV Increment 1			<0.005 EU/mg
DXSE-0123-00007-PV Increment 1			<0.005 EU/mg
DXSE-0123-00004-PV	Finished Good		<0.005 EU/mg
DXSE-0123-00006-PV			<0.005 EU/mg
DXSE-0123-00007-PV			<0.005 EU/mg

5.7. FREE SULFATE :

5.7.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Free Sulfate testing are detailed in the table below.

TABLE 7: FREE SULFATE

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor	<0.2%
DXSE-0123-00006-PV Pre-Filtration			<0.2%
DXSE-0123-00007-PV Pre-Filtration			<0.2%
DXSE-0123-00004-PV Post Filtration	Post Filtration		<0.2%
DXSE-0123-00006-PV Post Filtration			<0.2%
DXSE-0123-00007-PV Post Filtration			<0.2%
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	<0.2%	<0.2%
DXSE-0123-00006-PV Increment 1			<0.2%
DXSE-0123-00007-PV Increment 1			<0.2%
DXSE-0123-00004-PV	Finished Good		<0.2%
DXSE-0123-00006-PV			<0.2%
DXSE-0123-00007-PV			<0.2%

5.8. GLUCOSE CONTENT :

5.8.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Glucose Content testing are detailed in the table below.

TABLE 8: GLUCOSE CONTENT

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	35-48%	38%
DXSE-0123-00006-PV Pre-Filtration			36%
DXSE-0123-00007-PV Pre-Filtration			35%
DXSE-0123-00004-PV Post Filtration	Post Filtration		36%
DXSE-0123-00006-PV Post Filtration			36%
DXSE-0123-00007-PV Post Filtration			35%
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	35% - 48%	36%
DXSE-0123-00006-PV Increment 1			38%
DXSE-0123-00007-PV Increment 1			37%
DXSE-0123-00004-PV	Finished Good		37%
DXSE-0123-00006-PV			37%
DXSE-0123-00007-PV			36%

5.9. IDENTIFICATION TESTS :

5.9.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Identification testing are detailed in the table below.

TABLE 9: IDENTIFICATION TESTS

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor	Passes Test
DXSE-0123-00006-PV Pre-Filtration			Passes Test
DXSE-0123-00007-PV Pre-Filtration			Passes Test
DXSE-0123-00004-PV Post Filtration	Post Filtration		Passes Test
DXSE-0123-00006-PV Post Filtration			Passes Test
DXSE-0123-00007-PV Post Filtration			Passes Test
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	Passes Test	Passes Test
DXSE-0123-00006-PV Increment 1			Passes Test
DXSE-0123-00007-PV Increment 1			Passes Test
DXSE-0123-00004-PV	Finished Good		Passes Test
DXSE-0123-00006-PV			Passes Test
DXSE-0123-00007-PV			Passes Test

5.10. IRON

5.10.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Iron testing are detailed in the table below.

TABLE 10: IRON

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor	Refer to BSI-RPT-1438 for Elemental Impurity Assessment
DXSE-0123-00006-PV Pre-Filtration			
DXSE-0123-00007-PV Pre-Filtration			
DXSE-0123-00004-PV Post Filtration	Post Filtration		
DXSE-0123-00006-PV Post Filtration			
DXSE-0123-00007-PV Post Filtration			
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	2%	
DXSE-0123-00006-PV Increment 1			
DXSE-0123-00007-PV Increment 1			
DXSE-0123-00004-PV	Finished Good		
DXSE-0123-00006-PV			
DXSE-0123-00007-PV			

5.11. LOSS ON DRYING :

5.11.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Loss on Drying testing are detailed in the table below.

TABLE 11: LOSS ON DRYING

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor	77.6460%
DXSE-0123-00006-PV Pre-Filtration			77.9970%
DXSE-0123-00007-PV Pre-Filtration			78.0114%
DXSE-0123-00004-PV Post Filtration	Post Filtration		77.7432%
DXSE-0123-00006-PV Post Filtration			78.1144%
DXSE-0123-00007-PV Post Filtration			78.0635%
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	10% Max	7%
DXSE-0123-00006-PV Increment 1			8%
DXSE-0123-00007-PV Increment 1			7%
DXSE-0123-00004-PV	Finished Good		7%
DXSE-0123-00006-PV			8%
DXSE-0123-00007-PV			6%

5.12. **MANGANESE** :

5.12.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Manganese testing are detailed in the table below.

TABLE 12: MANGANESE

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor	Refer to BSI-RPT-1438 for Elemental Impurity Assessment
DXSE-0123-00006-PV Pre-Filtration			
DXSE-0123-00007-PV Pre-Filtration			
DXSE-0123-00004-PV Post Filtration	Post Filtration		
DXSE-0123-00006-PV Post Filtration			
DXSE-0123-00007-PV Post Filtration			
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	1 ppm max	
DXSE-0123-00006-PV Increment 1			
DXSE-0123-00007-PV Increment 1			
DXSE-0123-00004-PV	Finished Good		
DXSE-0123-00006-PV			
DXSE-0123-00007-PV			

5.13. **pH (FG - 1% SOLUTION; SOLUTION - 5% SOLUTION)** :

5.13.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the pH testing are detailed in the table below.

TABLE 13: pH

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor	7.23 @ 23.1°C
DXSE-0123-00006-PV Pre-Filtration			6.96 @ 23.1°C
DXSE-0123-00007-PV Pre-Filtration			7.45 @ 23.1°C
DXSE-0123-00004-PV Post Filtration	Post Filtration		7.21 @ 23.1°C
DXSE-0123-00006-PV Post Filtration			6.94 @ 23.1°C
DXSE-0123-00007-PV Post Filtration			7.27 @ 23.1°C
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	5.0- 7.5	7.2 @ 23.1°C
DXSE-0123-00006-PV Increment 1			6.9 @ 23.1°C
DXSE-0123-00007-PV Increment 1			7.2 @ 23.1°C
DXSE-0123-00004-PV	Finished Good		6.9 @ 23.6°C
DXSE-0123-00006-PV			6.9 @ 23.1°C
DXSE-0123-00007-PV			6.9 @ 23.1°C

5.14. RESIDUE ON IGNITION :

5.14.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Residue on Ignition testing are detailed in the table below.

TABLE 14: RESIDUE ON IGNITION

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor	9.6680%
DXSE-0123-00006-PV Pre-Filtration			9.2891%
DXSE-0123-00007-PV Pre-Filtration			9.5761%
DXSE-0123-00004-PV Post Filtration	Post Filtration		10.1009%
DXSE-0123-00006-PV Post Filtration			9.1956%
DXSE-0123-00007-PV Post Filtration			6.3340%
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	35 – 50%	40%
DXSE-0123-00006-PV Increment 1			39%
DXSE-0123-00007-PV Increment 1			41%
DXSE-0123-00004-PV	Finished Good		40%
DXSE-0123-00006-PV			39%
DXSE-0123-00007-PV			41%

5.15. PYRIDINE :

5.15.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Pyridine testing are detailed in the table below.

TABLE 15: PYRIDINE

Lot Number	Stage	Specification	Result
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor	1.38%
DXSE-0123-00006-PV Pre-Filtration			1.41%
DXSE-0123-00007-PV Pre-Filtration			1.61%
DXSE-0123-00004-PV Post Filtration	Post Filtration		1.63%
DXSE-0123-00006-PV Post Filtration			1.48%
DXSE-0123-00007-PV Post Filtration			1.49%
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment	NMT 2%	<2%
DXSE-0123-00006-PV Increment 1			<2%
DXSE-0123-00007-PV Increment 1			<2%
DXSE-0123-00004-PV	Finished Good		<2%
DXSE-0123-00006-PV			<2%
DXSE-0123-00007-PV			<2%

5.16. **RESIDUAL SOLVENTS** :

5.16.1. Refer to the Degradation and Impurity Protocol: Dextran Sulfate 8000 for testing methods and requirements. The results of the Residual Solvents testing are detailed in the table below.

TABLE 16: RESIDUAL SOLVENTS

Lot Number	Stage	Specification	Result	
			Methanol	IPA
DXSE-0123-00004-PV Pre-Filtration	Pre-Filtration, Post-Adjustment	Monitor for Methanol and Isopropyl Alcohol	<65280 ppm[2]	ND[1]
DXSE-0123-00006-PV Pre-Filtration			<73000 ppm[2]	ND[1]
DXSE-0123-00007-PV Pre-Filtration			<66143 ppm[2]	ND[1]
DXSE-0123-00004-PV Post Filtration	Post Filtration		<64187 ppm[2]	ND[1]
DXSE-0123-00006-PV Post Filtration			<64545 ppm[2]	ND[1]
DXSE-0123-00007-PV Post Filtration			<69486 ppm[2]	ND[1]
DXSE-0123-00004-PV Increment 1	1st Spray Dried Increment		2010 ppm	ND[1]
DXSE-0123-00006-PV Increment 1			1122 ppm	ND[1]
DXSE-0123-00007-PV Increment 1			966 ppm	ND[1]
DXSE-0123-00004-PV	Finished Good		1879 ppm	ND[1]
DXSE-0123-00006-PV			752 ppm	ND[1]
DXSE-0123-00007-PV			1120 ppm	ND[1]

[1] ND = None Detected

[2] Refer to Section 6.2.5.2 for further explanation.

6. CONCLUSION:

6.1. Multiple impurities were detected during the execution of the protocol, all finished goods samples met specification for required analysis indicating that the process successfully produces material with acceptable purity attributes.

6.2. Impurity information and characterization is discussed below including how the impurities (or objectionable characteristic such as color) were detected and what limits were set for the detected impurities or objectionable characteristic.

6.2.1. Appearance and Color:

6.2.1.1. Definition: A qualitative test describing the color of a solution and/or dry product.

6.2.1.2. Findings: Appearance and color was found to be more yellow prior to carbon treatment and filtration, this indicates there are unspecified impurities contributing negatively to color attributes in the starting 20% raw material. These unspecified impurities are controlled and reduced to appropriate levels throughout the process via filtration and quantitative release testing via UV-Vis absorbance at 360nm.

6.2.1.3. Limit: Limits for appearance and color are defined in DSXE-4250 product code.

6.2.2. Clarity:

6.2.2.1. Definition: A quantitative test describing the color of a solution and/or dry product.

6.2.2.2. Findings: Clarity was found to be higher prior to carbon treatment and filtration, this indicates there are unspecified impurities contributing negatively to clarity in the starting 20% raw material. These are controlled and reduced to appropriate levels throughout the process via filtration and quantitative release testing via UV-Vis absorbance at 360nm.

6.2.2.3. Limits: Limits for clarity are defined in the DXSE-4250 product code.

6.2.3. Loss on Drying:

6.2.3.1. Definition: A gravimetric test for volatile solvents.

6.2.3.2. Findings: The 20% solution contained between 70-80% volatile solvents, including water. This is controlled through the spray drying process and was reduced to acceptable levels.

6.2.3.3. Limits: Limits for loss on drying are defined in the DXSE-4250 product code.

6.2.4. Pyridine:

6.2.4.1. Definition: Pyridine (CAS 110-86-1) is a weak base and can be titrated with 0.1N hydrochloric acid (CAS 7647-01-0) with a 1:1 stoichiometric ratio. Exceeding the equivalence point with HCl yields complete neutralization of any residual pyridine in the dextran sulfate sample solution resulting in a pH of 2.8 or less (strongly acidic from excess HCl) when measured using a calibrated potentiometric pH meter.

6.2.4.2. Findings: Pyridine was detected in the raw materials at <2.0% meeting finished goods criteria based on the dried basis assessment and the finished goods also met acceptance criteria with a result of <2.0%.

6.2.4.3. Limits: Limits for pyridine are defined in the DXSE-4250 product code.

6.2.5. Residual Solvents:

6.2.5.1. Definition: A headspace GC-FID method of analysis to detect volatile organic compounds including methanol and isopropyl alcohol.

6.2.5.2. Findings: No isopropyl alcohol was detected at any stage of the process. Peaks were detected at the same retention time of methanol in the 20% solutions. This large peak was investigated by GC-MS for identification verification but was determined to be a mixture of methanol, pyridine, and phenol with contributed to the large area count detected in the initial analysis. The finished good was <0.3% (3,000ppm) for methanol indicating that all of the volatile organic compounds were reduced sufficiently through spray drying to meet DXSE-4250 specifications. The limit for phenol is not explicitly defined in the DXSE-4250 product code but by meeting purity requirements for sulfate (Sulfur) content and glucose content is ensures the purity of the dextran sulfate 8000 m.w. is not compromised due to excess phenol and is acceptable and requires no further controls for the DXSE-4250 specification.

6.2.5.3. Limits: The limit is acceptable for meeting requirements for residual solvents as tested and purity requirements for DXSE-4250 in the finished product.