BIOSPECTRA

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TECHNICALLY UNAVOIDABLE PARTICLE PROFILE (TUPP) TRIS HYDROCHLORIDE

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1. PURPOSE:

1.1. The purpose of this document is to provide the user of this product with a Technically Unavoidable Particle Profile (TUPP) for Tris Hydrochloride manufactured in Suite 3 at BioSpectra's Stroudsburg, PA facility.

2. SCOPE:

2.1. This TUPP applies to the manufacturing and packaging process of Tris Hydrochloride at BioSpectra's Stroudsburg, PA facility.

3. REFERENCES:

3.1. BSI-DGM-0012, FMEA & CE Matrix Template
3.2. BSI-FRM-0501, Contaminant Form
3.3. BSI-SOP-0006, Pre-Process Room Inspection SOP
3.4. BSI-SOP-0049, Equipment Preventative Maintenance
3.5. BSI-SOP-0057, Supplier, Manufacturer, and Service Provider Qualification Master Plan
3.6. BSI-SOP-0081, Written and Verbal Complaints
3.7. BSI-SOP-0084, Change Control
3.8. BSI-SOP-0102, Degradation and Impurity Profiling SOP
3.9. BSI-SOP-0137, Discrepancy Investigation Procedure
3.10. BSI-SOP-0435, Equipment Qualification Master Plan
3.11. IPEC Technically Unavoidable Particle Profile (TUPP) Guide

4. DEFINITIONS:

4.1. Atypical Particle: A visibly different particle that can be viewed with the naked eye, that is not consistent with a Technically Unavoidable Particle Profile (TUPP).
4.2. Contaminant: A visibly different particle that is not inherent of the process or is considered to be avoidable.
4.3. Technically Unavoidable Particle (TUP): A visibly different particle that can be viewed with the naked eye that is inherent to the raw material, manufacturing process or product and does not pose risk to patient safety.
4.4. Technically Unavoidable Particle Profiles (TUPPs): A report on all potential known Technically Unavoidable Particles (TUP) for an API or below grade process that can be shared with a customer or end user.
4.5. Typical Levels: Historical particulate levels seen in (product) produced at BioSpectra's Bangor, PA or Stroudsburg, PA facility and repackaged at BioSpectra's Bangor, PA facility that has been deemed as acceptable. If historical particulate levels are unavailable, then each particle will be classified utilizing a risk-based approach until a typical level can be established.
4.6. Typical Sizes: Historical particle sizes seen in (product) produced at BioSpectra's Bangor, PA or Stroudsburg, PA facility. If historical particulate sizes are unavailable, then the lowest insoluble matter specification available will be utilized as the maximum allowable particulate size.
4.7. Technically Unavoidable Particles (TUP):
    4.7.1. Technically unavoidable particles that may be present in GMP processes producing API Finished Goods or below are investigated and assessed to ensure there is no risk to the quality of the finished good material. This SOP is not applicable to objectionable particles resulting from contamination or adulteration.
    4.7.2. Particles typically described as Technically Unavoidable Particles:
        4.7.2.1. A study should be initiated into the raw material, manufacturing and packaging processes to identify particles.
            4.7.2.1.1. Charred Particles:

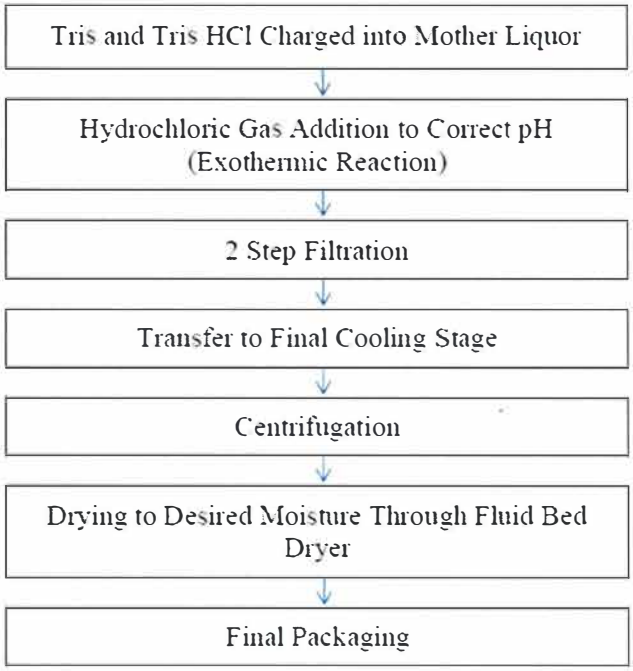
4.7.2.1.1.1. Discolored due to heat or friction.
4.7.2.1.2. Materials of Construction (MOC):
4.7.2.1.2.1. From manufacturing equipment that is product contacting or known to have normal and expected wear.
4.7.2.1.2.2. From packaging components.
4.7.2.1.2.3. Documented Risk Assessments for these are available in the associated FMEA and individual product TUPPs.
4.7.2.1.3. Routinely used gaskets, seals, filters, etc.
4.7.2.1.3.1. Expected to have normal wear.
4.7.2.1.4. Lubricants, greases, oils or like materials.
4.7.2.1.4.1. Discolored due to traces of such materials.
4.7.2.1.4.2. Should be approved for use as Food grade or food contact grade or justified otherwise.
4.7.2.1.5. Misshapen or morphologically distinct particles.
4.7.2.1.6. Compressions/agglomerations, elongated/tangles or flakes.
4.7.2.1.7. Color variation inherent of the product.
4.7.2.1.7.1. Intrinsic components carried through from raw materials.
4.7.2.1.7.2. Mined or sourced from natural products.

5. TECHNICALLY UNAVOIDABLE PARTICLES (TUP):

5.1. The construction of a technically unavoidable particle profile assumes that GMPs are followed and possible mitigation strategies are taken, the remaining particles, if they pose no risk to safety, are deemed technically unavoidable.

5.2. Technically unavoidable particles could originate from any of the following parts of the manufacturing process: Material of Construction of the manufacturing equipment that is product contacting, consumable process equipment, Material of Construction of the packaging components and any materials that are involved in the manufacturing process that may come into contact with the product that are the lowest risk scenarios

6. PROCESS FLOW DIAGRAM:



7. PROFILE:

7.1. Manufacturing Location:
  7.1.1. Stroudsburg, PA Facility
7.2. Applicable Product Codes:
  7.2.1. THCL-3200 and below grades
7.3. TUPPs originating from product contacting surfaces in the manufacturing

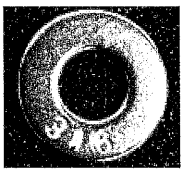
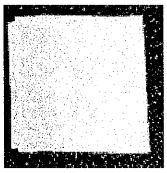
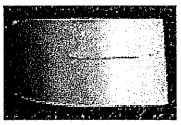
Table 1: Originating from the Manufacturing process								
Identity	Characterization	Origin	Source of Particulate	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
316 Stainless Steel	Metal Shaving	Tank agitator, centrifuge, centrifugal pumps screw conveyor, dryer, scoops, Filter Housing	Shaft, blades, screw conveyor, hopper and grate, dryer, centrifuge basket, pump impeller and housing scoops	Filtration, inspection	Two stage filtration, Pre-Process room Inspection, Preventative Maintenance		≤0.05mm	Not Expected - Low Level
Hastelloy	Metal Shaving	Slurry Tank, Tank Piping, Hoses	Slurry Tank 03 Agitator, Pipe fittings, Sanitary hose ends.	Inspection	Pre-Process room Inspection, Preventative Maintenance		≤0.05mm	Not Expected - Low Level
Silicone	Clear, white, orange Semi-transparent elastomer fragment	Centrifuge, filter housing, piping gaskets	Gaskets	Filtration, Inspection	Pre-Process room Inspection, Preventative Maintenance		≤1mm	Not Expected - Low Level
CLPE	Colored plastic	Process Tank, Slurry Tank, piping	Process Tank, Slurry Tank, centrifuge piping	Inspection	Preventative Maintenance Inspection	Not Applicable	≤2mm	Not Expected - Low Level
CPVC	Gray plastic	Process Tank, ML Holding Tote, fittings, piping, Filter Housing	Process Tank, Piping	Filtration	Two stage filtration, Pre-Process room Inspection		≤2mm	Not Expected - Low Level
HDPE	White plastic	Dryer, ML Holding Tote, Slurry Tank	Walls of dryer, Piping, Tank and Lid	Inspection	Pre-Process room Inspection, Preventative Maintenance		≤2mm	Not Expected - Low Level
PVDF (Kynar)	White, off white plastic	Centrifuge, slurry tank, centrifugal pump, ML Holding Tote, Filter Housing	Process piping	Inspection	Pre-Process room Inspection, Preventative Maintenance	Not Applicable	≤2mm	Not Expected - Low Level

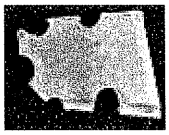
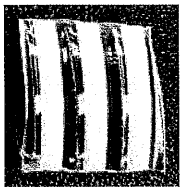
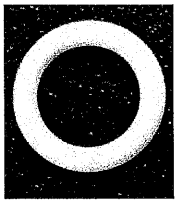
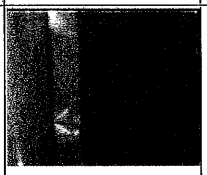
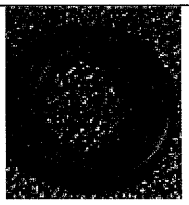
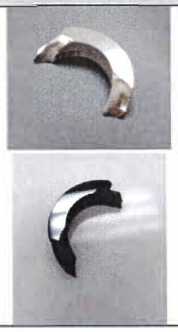
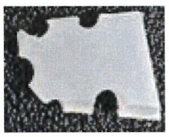
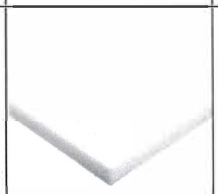
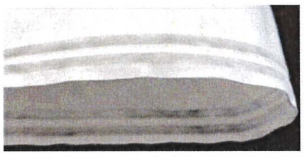
Table 1: Originating from the Manufacturing process								
Identity	Characterization	Origin	Source of Particulate	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
Polypropylene	Semi-opaque to off-white plastic, yellow or black plastic,	ML Holding Tote, Filter Housing, pumps, centrifuge, piping	Tank, valve seats, manifolds, basket screen, cloth, piping	Filtration, inspection	Two stage filtration, Pre-Process room Inspection , Preventative Maintenance		≤2mm	Not Expected - Low Level
PVC	White, black or grey plastic	Piping, flanges, hoses	Centrifuge, dryer, Screw Conveyor	Filtration, inspection	Two stage filtration, Pre-Process room Inspection, Preventative Maintenance		≤2mm	Not Expected - Low Level
Teflon	Opaque white plastic, white plastic, white thread	ML Tank, pumps, centrifuge, Screw Conveyor, dryer, Filter Housing	Gaskets, o-rings, diaphragms, Screw Conveyor Hopper agitator seals	Filtration, inspection	Two stage filtration, Pre-Process room Inspection, Preventative Maintenance		≤2mm	Not Expected - Low Level
LLDPE	Clear plastic	Bin liners	Liner	Inspection	Pre-Process room Inspection		≤2mm	Not Expected - Low Level
Viton	Black Elastomer Fragment	Slurry Tank, Pump, Screw Conveyor, Filter Housing	Gaskets	Filtration, inspection	Two stage filtration, Pre-Processroom Inspection		≤1mm	Not Expected - Low Level
Carbon	Black or Gray Fragments	Centrifugal Pump	Centrifugal Pump Shaft Seal	3-Step Purification, Reprocessing	Pre-Process Inspection, Preventative Maintenance		≤0.05mm	Not Expected - Low Level

Table 1: Originating from the Manufacturing process								
Identity	Characterization	Origin	Source of Particulate	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
Silicon Carbide	CeramicFragment	Centrifugal Pump	Stationary Seat of seal	3-Step Purification, Reprocessing	Pre-Process Inspection, Preventative Maintenance		≤0.05mm	Not Expected - Low Level
TPV	Thermoplastic	Diaphragm Pump	Diaphragm	Reprocessing	Pre-Process Inspection, Preventative Maintenance		<0.5	Not Expected, Low Level
Extren	Fiberglass Structure	Dryer	Dryer frame	3-Step Purification, Reprocessing	Pre-Process Inspection, Preventative Maintenance		<.02mm	Not Expected
Polycarbonate	Transparent Thermoplastic	Dryer	Sight glass	Reprocessing	Pre-Process Inspection, Preventative Maintenance		<0.5	Low Level
Polyethylene	Thermoplastic polymer	ML Holding Tank, Dryer, Screw Conveyor, Slurry Tank	ML Holding Tank, Dryer Bed, Screw Tube, Piping	Reprocessing	Pre-Process Inspection, Preventative Maintenance		<0.4	Low Level

7.4. TUPPs originating from product contacting surfaces of the packaging components:

7.4.1. The following TUPPs are dependent on the packaging type.

Table 2: Originating from the Packaging components

Identity	Characterization	Origin	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
LLDPE	Clear Plastic	Liner (Packaging)	Inspection at time of use	Inspection at time of use		≤2mm	Not Expected - Low Level
Tyvek	White Plastic	Tyvek Liner	Reprocessing	Inspection at time of use		≤2mm	Not Expected - Low Level
HDPE	White Plastic	Bottle (Packaging)	Reprocessing	Inspection at time of use		≤2mm	Not Expected - Low Level
Polypropylene	Blue Plastic	Tamper Evident lid (Packaging)	Reprocessing	Inspection at time of use		≤2mm	Not Expected - Low Level

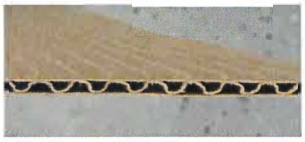
7.5. Atypical particles originating from non-product contacting surfaces for potable water.

Table 3: Originating from Manufacturing Equipment					
Identity	Characterization	Origin	How Removed	How Prevented	Picture
Aluminum, Plastic, Brass, Copper, Steel, Stainless Steel, Manufacturer provided Elastomers.	Plastic, Metal, and Elastomer Shavings	Potable Water Hose Nozzle	Reprocessing	Inspection at time of use	

7.6. Atypical particles originating from non-product contacting surfaces of the packaging components:

7.6.1. The following Atypical particles are dependent on the packaging type.

Table 4: Originating from the Packaging components					
Identity	Characterization	Origin	How Removed	How Prevented	Picture
HMW-HDPE	Blue Plastic	Drum (Packaging)	Reprocessing	Inspection at time of use	
HDPE	Blue or White Plastic	Pail and Lid (Packaging)	Reprocessing	Inspection at time of use and Product Care Procedure	

Table 4: Originating from the Packaging components					
Identity	Characterization	Origin	How Removed	How Prevented	Picture
Fiber	Brown cardboard	Drum (Packaging) Drum (Desiccant Storage)	Inspection at time of use	Inspection at time of use	
Cardboard	Brown	Pallet Liner	Inspection at time of use	Inspection at time of use	
Wood	Wood Shaving	Pallet	Inspection at time of use	Inspection at time of use