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TECHNICALLY UNAVOIDABLE PARTICLE PROFILE (TUPP) TRIS HYDROCHLORIDE – M11

TABLE OF CONTENTS

1. PURPOSE:.....	3
2. SCOPE:.....	3
3. REFERENCES:.....	3
4. DEFINITIONS:	3
5. TECHNICALLY UNAVOIDABLE PARTICLES (TUP):.....	4
6. PROCESS FLOW DIAGRAM:	4
7. PROFILE:	5

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 process room M11 at BioSpectra's Bangor, PA facility.

2. SCOPE:

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

3. REFERENCES:

- 3.1. BSI-DGM-0012, FMEA & CE Matrix Template
- 3.2. BSI-FRM-0501, Contaminant Form
- 3.3. BSI-FRM-0821, Change Control Form
- 3.4. BSI-FRM-0922, In-process Contaminant Form
- 3.5. BSI-SOP-0006, Pre-Process Room Inspection SOP
- 3.6. BSI-SOP-0049, Equipment Preventative Maintenance
- 3.7. BSI-SOP-0057, Supplier, Manufacturer, and Service Provider Qualification Master Plan
- 3.8. BSI-SOP-0081, Written and Verbal Complaints
- 3.9. BSI-SOP-0102, Degradation and Impurity Profiling SOP
- 3.10. BSI-SOP-0137, Discrepancy Investigation Procedure
- 3.11. BSI-SOP-0435, Equipment Qualification Master Plan
- 3.12. IPEC Technically Unavoidable Particle Profile (TUPP) Guide

4. DEFINITIONS:

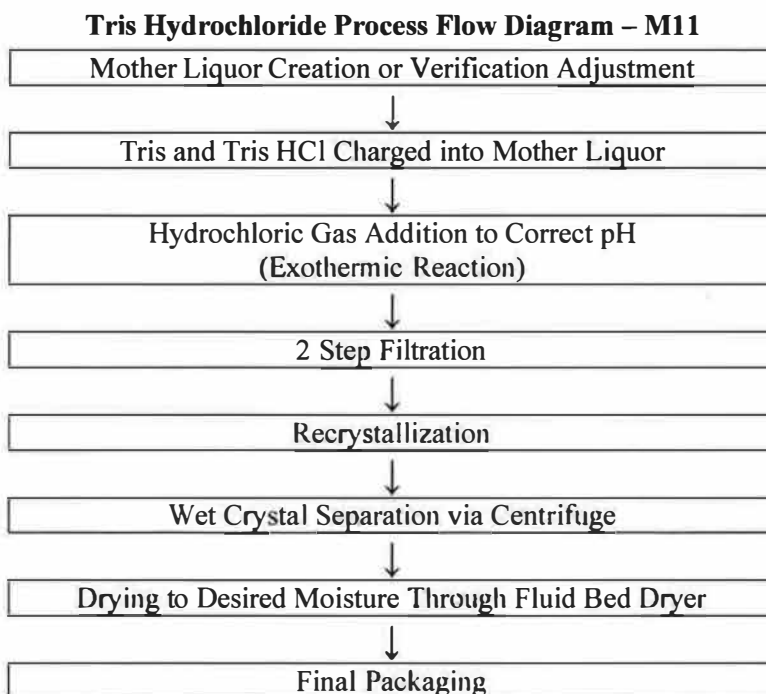
- 4.1. Atypical Particle: A visibly different particle that can be viewed with the naked eye, that is not consistent with a Technically Unavoidable Particle Profile (TUPP).
- 4.2. Contaminant: A visibly different particle that is not inherent of the process or is considered to be avoidable.
- 4.3. Technically 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:



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7. **PROFILE:**



7.1. Manufacturing Location:

7.1.1. Bangor, PA Facility







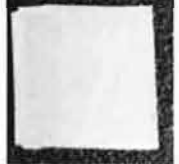
7.2. Applicable Product Codes:

7.2.1. THCL-3200 and below compliance grades

7.3. TUPPs originating from product contacting surfaces in the manufacturing

Originating from the Process Equipment							
Identity	Characterization	Origin	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
316 Stainless Steel	Metal Shaving	Centrifuge, Hopper, Fluid Bed Dryers, Centrifugal Pumps, Vacuum Conveyor	Filtration, inspection	Two stage filtration, Pre-Process room Inspection, Preventative Maintenance		≤0.05mm	Not Expected - Low Level
Hastelloy	Metal Shaving	Tank Agitators	Inspection	Pre-Process room Inspection, Preventative Maintenance		≤0.05mm	Not Expected - Low Level
Silicone	Clear, white, orange Semi-transparent elastomer fragment	Fluid Bed Dryers, Gaskets	Filtration, Inspection	Pre-Process room Inspection, Preventative Maintenance		≤1mm	Not Expected - Low Level
PVC	White / Gray / Black Plastic	Fluid Bed Dryers, Flanges, Milk Hoses, Vacuum Conveyor Hose, Fluid Bed Dryer Hoses	Inspection	Pre-Process room Inspection		≤2mm	Not Expected - Low Level
CPVC	White / Gray / Black Plastic	Piping & Fittings, Wands,	Inspection	Pre-Process room Inspection		≤2mm	Not Expected - Low Level
HDPLE	White or Black Plastic	Mother Liquor Holding Tanks, Process Tank, Slurry Tanks	Filtration, inspection	Two stage filtration, Pre-Process room Inspection, Preventative Maintenance		≤0.05mm	Not Expected - Low Level
UHMW-PE	Semi-opaque to off-white plastic, Purple Plastic	Chemical Hoses	Filtration, Inspection	Pre-Process room Inspection, Preventative Maintenance		≤1mm	Not Expected - Low Level
Polypropylene	Semi-opaque to off-white plastic, yellow or black plastic,	Basket Filters, Diaphragm Pumps, Centrifuge Cloths	Filtration, Inspection	Pre-Process room Inspection, Preventative Maintenance		≤1mm	Not Expected - Low Level





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Originating from the Process Equipment							
Identity	Characterization	Origin	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
HDPE	White plastic	Fluid Bed Dryers, Collection Bins, Scoops/Shovels	Inspection	Pre-Process room Inspection		≤2mm	Not Expected - Low Level
Teflon (PTFE)	Opaque white plastic, white plastic, white thread	Diaphragm Pumps, Gaskets, Threaded Piping and Connections	Filtration, Inspection	Pre-Process room Inspection, Preventative Maintenance		≤2mm	Not Expected - Low Level
LLDPE	Clear plastic	Bin liners	Inspection	Pre-Process room Inspection		≤2mm	Not Expected - Low Level
Viton	Black Elastomer Fragment	Gaskets	Filtration, Inspection	Two stage filtration, Pre-Process room Inspection		≤1mm	Not Expected - Low Level
Carbon	Black or Gray Fragments	Centrifugal Pumps	Filtration, Inspection	Two stage filtration, Pre-Process room Inspection		≤0.05mm	Not Expected - Low Level
BUNA	Black Elastomer Fragment	Gaskets	Filtration, Inspection	Two stage filtration, Pre-Process room Inspection		≤1mm	Not Expected - Low Level
Polyethylene	Semi-opaque to off-white plastic	Gas Delivery Lines	Inspection	Pre-Process room Inspection		≤1mm	Not Expected - Low Level

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

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

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 of the packaging components:

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

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	
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	