BIOSPECTRA
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TECHNICALLY UNAVOIDABLE PARTICLE PROFILE (TUPP) - GUANIDINE HYDROCHLORIDE MANUFACTURING IN S05 AT THE STROUDSBURG, PA MANUFACTURING FACILITY

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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 Guanidine Hydrochloride manufactured in Process Suite 5 at BioSpectra's Stroudsburg, PA manufacturing facility.

2. SCOPE:

2.1. This TUPP applies to the manufacturing and packaging process of Guanidine 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 Particles: 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 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 Stroudsburg, PA facility and repackaged at BioSpectra's Bangor, PA facility. If historical particulate sizes are unavailable, then the lowest insoluble matter specification will be utilized as the maximum allowable particulate size.

5. TECHNICALLY UNAVOIDABLE PARTICLES (TUP):

5.1. 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.

5.2. Particles typically described as Technically Unavoidable Particles:

5.2.1. A study should be initiated into the raw material, manufacturing and packaging processes to identify particles.

5.2.1.1. Charred Particles:

5.2.1.1.1. Discolored due to heat or friction.

5.2.1.2. Materials of Construction (MOC):

5.2.1.2.1. From manufacturing equipment that is product contacting or known to have normal and expected wear.

5.2.1.2.2. From packaging components.

5.2.1.2.3. Documented Risk Assessments for these are available in the associated FMEA and individual product TUPPs.

5.2.1.3. Routinely used gaskets, seals, filters, etc.

5.2.1.3.1. Expected to have normal wear.

5.2.1.4. Lubricants, greases, oils or like materials.

5.2.1.4.1. Discolored due to traces of such materials.

5.2.1.4.2. Should be approved for use as food grade or food contact grade or justified otherwise.

5.2.1.5. Misshapen or morphologically distinct particles.

5.2.1.5.1. Compressions/agglomerations, elongated/tangles or flakes.

5.2.1.6. Color variation inherent of the product.

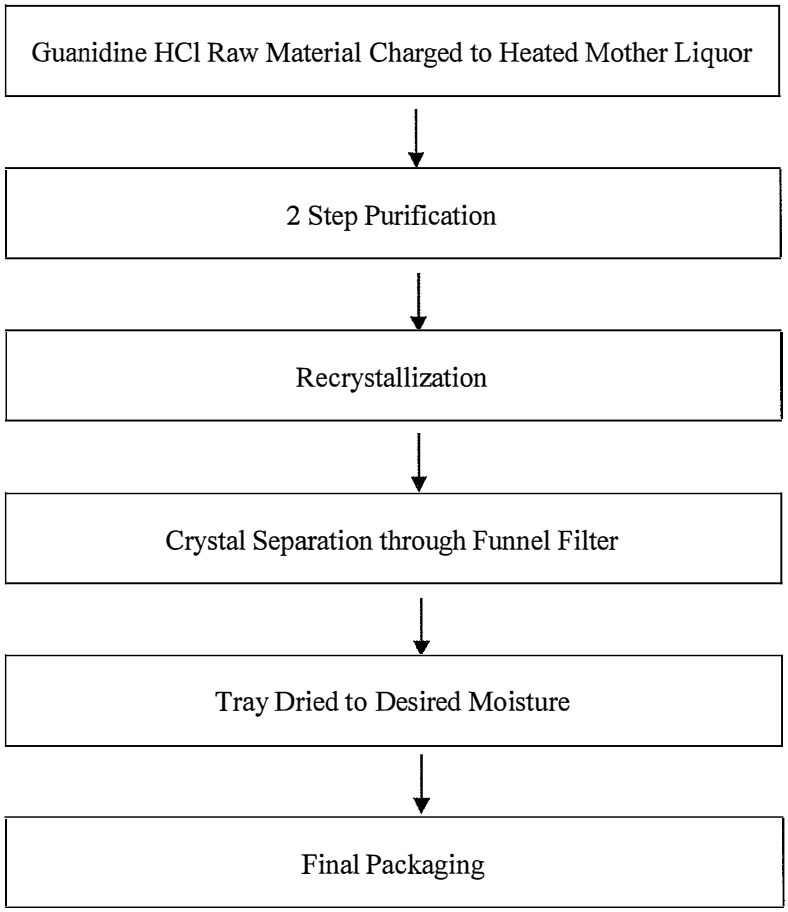
5.2.1.7. Intrinsic components carried through from raw materials.

5.2.1.7.1. Mined or sourced from natural products.

5.3. 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.

5.4. 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. Process Suite 5 at BioSpectra's Stroudsburg, PA manufacturing facility

7.2. Applicable Product Codes:

7.2.1. All Guanidine Hydrochloride product codes

7.3. TUPPs originating from product contacting surfaces in the manufacturing process:

Table 1 Originating from the Process Suite

Identity	Characterization	Origin	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
316 Stainless Steel	Metallic Shaving	Portable Sprayer Tank, Tray Sifter, Zeta Filter Housing and piping, Cartridge Filter Lid, Centrifugal PumpImpeller / Pump Head / Back Plate	Inspection of the product (Post-Filtration)	Pre-Process Inspection, Preventative Maintenance and Centrifugal Pump Pre and Post Filtration		≤0.5mm	Not Expected – LowLevel
Carbon	Black or Gray Fragments	Centrifugal PumpShaft Seal	Inspection of the product	Pre-Process Inspection, Preventative Maintenance		≤0.5mm	Not Expected – LowLevel
Cellulose	Brown like cardboard	Zeta filter media/ Poly Liner Packaging	Inspection of the product	Filter inspection, caps for liner rolls		≤2mm	Not Expected – Low Level
SiliconCarbide	Ceramic Fragment	Centrifugal PumpShaft Seal	Inspection of the product	Pre-Process Inspection, Preventative Maintenance and Centrifugal Pump Pre and Post Filtration		≤0.5mm	Not Expected – LowLevel
CLPE	Semi-translucent Plastic	Cold Tank - Tank	2 Step Purification, Inspection of the product	Pre-Process Inspection, Preventative Maintenance	Not Applicable	≤2mm	Not Expected – LowLevel
CPVC	Gray Plastic	Cold Tank Piping	2 Step Purification (Pre-filtration)	Pre-Process Inspection, Preventative Maintenance		≤2mm	Not Expected – LowLevel
		Diaphragm PumpPiping, Cartridge Filter Body / Piping / Valves, Funnel FilterPiping	Inspection of the product (Post-Filtration)				

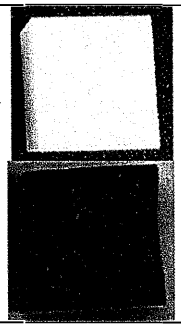
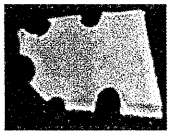
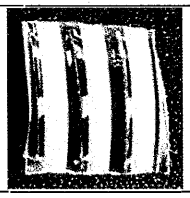
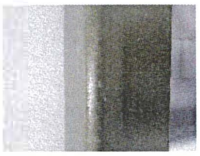
Table 1 Originating from the Process Suite							
Identity	**Characterization**	**Origin**	**How Removed**	**How Prevented**	**Picture**	**Typical Sizes**	**Typical Levels**
Glass	Glass Fragment	Heat Exchanger –Body	2 Step Purification, Inspection of the product	Pre-Process Inspection, Preventative Maintenance	Not Applicable	≤1mm	Not Expected – Low Level
Hastelloy C276	Metallic Shaving	Cold Tank Agitator Shaft and Blade, Hot Tank Agitator Shaft and Blade, Spider bolts	2 Step Purification, Inspection of the product	Pre-Process Inspection, Preventative Maintenance		≤0.5mm	Not Expected – Low Level
HDPE	White or Black Plastic	Cold Tank Lid	2 Step Purification, Inspection of the product	Pre-Process Inspection, Preventative Maintenance		≤2mm	Not Expected – Low Level
		Funnel Filter Support Structure	Inspection of the product (Post-Filtration)				
Kynar	Translucent Natural Plastic	Heat Exchanger Piping and Valves	2 Step Purification, Inspection of the product	Pre-Process Inspection, Preventative Maintenance	Not Applicable	≤2mm	Not Expected – Low Level
		Funnel Filter Piping, Zeta Filter Piping, Diaphragm PumpPiping, Cartridge Filter Piping	Inspection of the product				
Polypropylene	Natural Colored Opaque Off-White, Blue Plastic	Diaphragm Pump Fluid Covers / Manifolds / Check Valve Seats, Funnel Filter and Perforated Plate, Pulsation Dampener Body, Process Piping, Scoop/Shovel, Drying Trays	Inspection of the product	Pre-Process Inspection, Preventative Maintenance		≤2mm	Not Expected – Low Level
PVC	White, Clear, or Gray Opaque Plastic	Portable Sprayer Hose, Pulsation Dampener Piping, Spider	Inspection of the product	Pre-Process Inspection, Preventative Maintenance		≤2mm	Not Expected – Low Level

Table 1 Originating from the Process Suite							
Identity	**Characterization**	**Origin**	**How Removed**	**How Prevented**	**Picture**	**Typical Sizes**	**Typical Levels**
Teflon	Opaque white plastic	Pulsation Dampener Diaphragm, Diaphragm PumpCheck Valve Balls/Diaphragm	Inspection of the product	Pre-Process Inspection, Preventative Maintenance		≤2mm	Not Expected – Low Level
		Heat Exchanger Piping, Piping Gaskets	2 Step Purification, Inspection of the product				
XLPE	Semi-translucentOff-white Plastic	Hot Tank - Tank	2 Step Purification, Inspection of the product	Pre-Process Inspection, Preventative Maintenance	Not Applicable	≤2mm	Not Expected – Low Level
Viton	Black Elastomer Fragment	Centrifugal PumpGasket, Piping Gaskets	2 Step Purification, Inspection of the product	Pre-Process Inspection, Preventative Maintenance and Centrifugal Pump Pre and Post Filtration		≤1mm	Not Expected – Low Level
Silicone	Clear or White Elastomer	Piping Gasket	Inspection of the product	Pre-Process Inspection, Preventative Maintenance		≤1mm	Not Expected – Low Level
EPDM	Black Elastomer	Diaphragm Pump Gasket, Ball Valves	2 Step Purification, Inspection of the product	Pre-Process Inspection, Preventative Maintenance		≤1mm	Not Expected – Low Level
Vinyl plastic	Blue	Sanitary fitting cover	Inspection at time of use	Inspection at time of use		≤2mm	Not Expected – Low Level
Extren Fiberglass	Green	Spider, structure support	Inspection at time of use	Pre-Process Inspection, Preventative Maintenance		≤2mm	Not Expected – Low Level

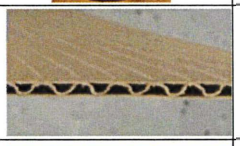
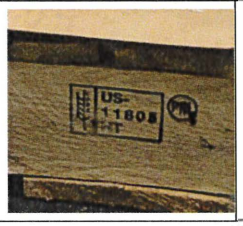
7.4. TUPPs originating from product contacting surfaces of the packaging components:

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**	**TypicalLevels**
Hexene LLDPE	Clear Plastic	Liner (Packaging)	Inspection at time of use	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.

Table 3 Originating from the Packaging Components							
Identity	**Characterization**	**Origin**	**How Removed**	**How Prevented**	**Picture**	**Typical Sizes**	**Typical Levels**
Fiber	Brown cardboard	Drum (Packaging), Drum (Desiccant Storage)	Inspection at time of use	Inspection at time of use		≤2mm	Not Expected – Low Level
Cardboard	Brown	Pallet Liner	Inspection at time of use	Inspection at time of use		≤2mm	Not Expected – Low Level
Wood	Wood Shaving	Pallet	Inspection at time of use	Inspection at time of use		≤2mm	Not Expected– Low Level

7.6. Atypical particles originating from personal protective equipment (PPE) or manufacturing uniforms:

Table 4 Originating from PPE/Uniforms

Identity	Characterization	Origin	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
Nitrile	Blue	Gloves	Inspection at time of use	Inspection at time of use		≤2mm	Not Expected – Low Level
Tyvek	White	Disposable Lab Jackets, Coveralls, PAPRs and Sleeves	Inspection at time of use	Inspection at time of use		≤2mm	Not Expected – Low Level
Polyester	Blue and Black Fibers	Manufacturing Uniform and PAPRs	Inspection at time of use	Inspection at time of use		≤2mm	Not Expected – Low Level