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TECHNICALLY UNAVOIDABLE PARTICLE PROFILE
(TUPP) – TRIS MANUFACTURED IN PROCESS
SUITE 1, SUITE 2 AND SUITE 4 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 Tris manufactured in Process Suite 1, Process Suite 2 and Process Suite 4 at BioSpectra's Stroudsburg, PA manufacturing facility.

2. SCOPE:

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

3. REFERENCES:

- 3.1. IPEC; Technically Unavoidable Particle Profile (TUPP) Guide

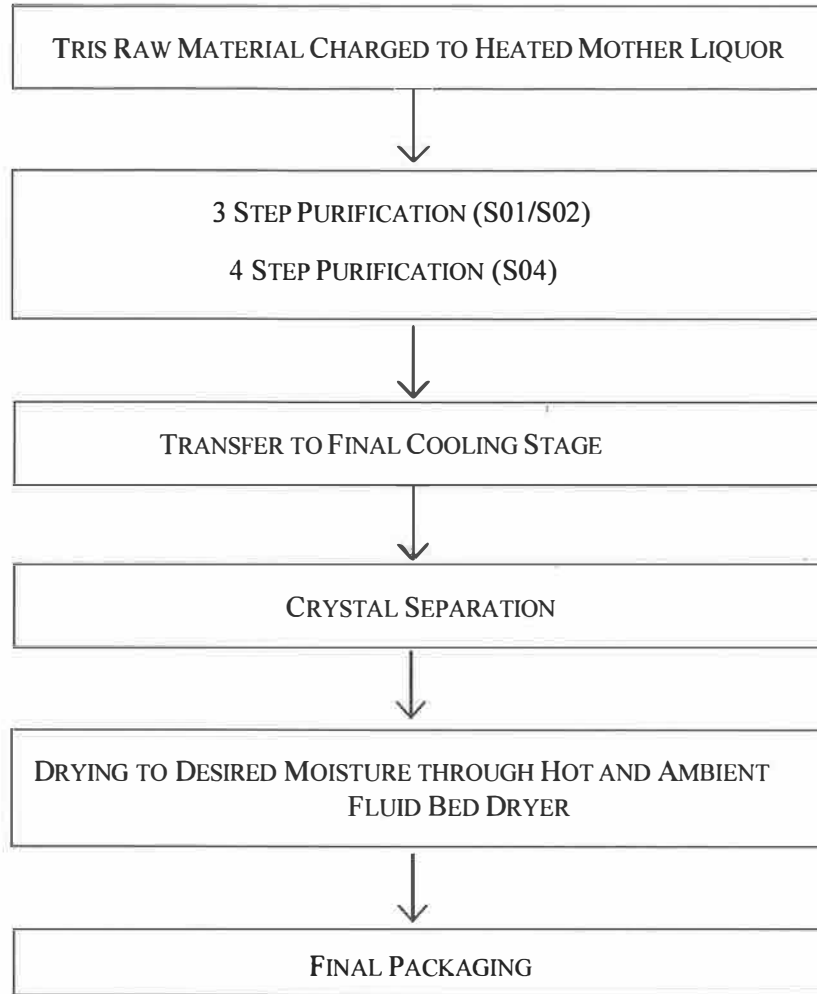
4. DEFINITIONS:

- 4.1. 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.
- 4.2. Technically Unavoidable Particle Profiles (TUPPs): A report on all potential known Technically Unavoidable Particles (TUP) for an excipient process that can be shared with a customer or end user.
- 4.3. Atypical Particles: Particles not consistent with the typical particulate profile; not previously encountered or identified.
- 4.4. Reprocessing: A system of improving an intermediate or finished product that does not conform to established specification by repeating a step or series of steps that are a part of the approved manufacturing process. The reprocessing of a batch of Tris was approved as part of the validation of the Tris manufacturing process.

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. Scenarios that are considered to be the lowest risk are situations in which no mitigation strategies exist or cannot be implemented within reason.

6. PROCESS FLOW DIAGRAM:



7. PROFILE:

7.1. Manufacturing Location:



7.1.1. Process Suite 1, Process Suite 2 and Process Suite 4 in BioSpectra’s Stroudsburg, PA Manufacturing Facility

7.2. Applicable Product Codes:




7.2.1. All TRIS product codes

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





Originating from the S01/S02 Manufacturing Process Suite

| Identity | Characterization | Origin | How Removed | How Prevented | Picture | Typical Sizes | Typical Levels |
|-----------------|--------------------------|---|--|--|---|---------------|--------------------------|
| Cellulose | Fiber | Filtration (Filtermedia) | 3-Step Purification, Reprocessing | Replacement of Filters, Inspection |  | ≤1MM | NOT EXPECTED - LOW LEVEL |
| Silica | White Powder | Filtration (Filtermedia) | 3-Step Purification, Reprocessing | Replacement of Filters, Inspection |  | ≤1MM | NOT EXPECTED - LOW LEVEL |
| Carbon | Black particle | Filtration (Filter media) Centrifugal Pump Shaft Seal | 3-Step Purification, Reprocessing | Replacement of Filters, Inspection | Not Available | ≤0.05MM | NOT EXPECTED - LOW LEVEL |
| UHMW PE | White Plastic | Screw Feeder Tube | Reprocessing | Pre-Process Inspection, Preventative Maintenance | Not Available | ≤2MM | NOT EXPECTED - LOW LEVEL |
| PTFE | White Plastic | Diaphragm Pump, Filter Gaskets, Sanitary Piping Gaskets | 3-Step Purification, Reprocessing | Replacement of Filters, Pre-Process Inspection, Preventative Maintenance |  | ≤2MM | NOT EXPECTED - LOW LEVEL |
| Silicon Carbide | Ceramic Fragment | Centrifugal Pump Stationary Seat | 3-Step Purification, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤0.05MM | NOT EXPECTED - LOW LEVEL |
| Viton | Black elastomer fragment | Pumps (O-rings, gaskets) Process piping | 3-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤1MM | NOT EXPECTED - LOW LEVEL |

Originating from the S01/S02 Manufacturing Process Suite




| Identity | Characterization | Origin | How Removed | How Prevented | Picture | Typical Sizes | Typical Levels |
|----------------|--|--|--|---|---|---------------|--------------------------|
| Poly-propylene | Natural colored opaque, opaque off-white, blue plastic | ML Totes Funnel Filter Pumps Product shovel Centrifuge Mesh cloth Filter Media Diaphragm Pump Piping/ Fluid Covers/ Manifolds/ Check Valve Seats ML Return Tank | 3-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤2MM | NOT EXPECTED - LOW LEVEL |
| PVC | White, Clear, Opaque plastic | ML Tote Process hose (Fittings) Centrifuge ML Return Cyclone Exhaust Duct Dryer Exhaust Duct Portable Sprayer Piping Screw Conveyor Hose Centrifuge Wash Tank Piping | 3-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤2MM | NOT EXPECTED - LOW LEVEL |
| Silicone | Clear plastic, Orange elastomer fragment | Funnel Filter Gaskets Dryer Bed | Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤1MM | NOT EXPECTED - LOW LEVEL |



Originating from the S01/S02 Manufacturing Process Suite

| Identity | Characterization | Origin | How Removed | How Prevented | Picture | Typical Sizes | Typical Levels |
|---------------------|------------------|---|---|---|---|---------------|-----------------------------------|
| Stainless Steel 316 | Metallic shaving | Process Tank Piping Agitator Blade/ Shaft Filter Housing Filter Basket Filter Piping Centrifuge Basket Centrifuge ML Return Centrifugal Pump Head/ Impeller/ Back Plate Diaphragm Pump Piping Dryer Body/Bed Portable Sprayer Screw Conveyor Flytes/ Cover/ Hopper/ Grate/ Hardware Centrifuge Wash Tank/ Piping | 3-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤0.05MM | NOT EXPECTED - LOW LEVEL |
| Stainless Steel 304 | Metallic shaving | Process Tank/ Lid | 3-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤0.05MM | NOT EXPECTED - LOW LEVEL |
| Poly-carbonate | Clear Plastic | Centrifuge Sight Glass Cyclone | 3-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance | Not Available | ≤2MM | NOT EXPECTED - LOW LEVEL |
| HDPE | White HDPE | Centrifuge Sight Glass, Funnel Filter, Screw Conveyor | 3-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤2MM | NOT EXPECTED - LOW LEVEL |
| CPVC | Gray Plastic | ML Return Tank Piping | 3-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤2MM | NOT EXPECTED - LOW LEVEL |

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| Originating from the S04 Manufacturing Process Suite | | | | | | | |
|--|--------------------------|--|--|--|---|---------------|--------------------------|
| Identity | Characterization | Origin | How Removed | How Prevented | Picture | Typical Sizes | Typical Levels |
| Cellulose | Fiber | Filtration (Filter media) | 4-Step Purification, Reprocessing | Replacement of Filters, Inspection |  | ≤1MM | NOT EXPECTED - LOW LEVEL |
| Silica | White Powder | Filtration (Filter media) | 4-Step Purification, Reprocessing | Replacement of Filters, Inspection |  | ≤1MM | NOT EXPECTED - LOW LEVEL |
| Carbon | Black particle | Filtration (Filter media) Centrifugal Pump Shaft Seal, Tank agitator seals | 4-Step Purification, Reprocessing | Replacement of Filters, Inspection |  | ≤0.05MM | NOT EXPECTED - LOW LEVEL |
| UHMW PE | White Plastic | Screw Feeder Tube | Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤2MM | NOT EXPECTED - LOW LEVEL |
| PTFE | White Plastic | Filter Gaskets, Sanitary Piping Gaskets, Centrifuge Gaskets | 4-Step Purification, Reprocessing | Replacement of Filters, Pre-Process Inspection, Preventative Maintenance |  | ≤2MM | NOT EXPECTED - LOW LEVEL |
| Silicon Carbide | Ceramic Fragment | Centrifugal Pump Stationary Seat | 4-Step Purification, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤0.05MM | NOT EXPECTED - LOW LEVEL |
| Viton | Black elastomer fragment | Pumps (O-rings, gaskets) Process piping gaskets | 4-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤1MM | NOT EXPECTED - LOW LEVEL |

| Originating from the S04 Manufacturing Process Suite | | | | | | | |
|--|---|---|--|--|---|---------------|--------------------------|
| Identity | Characterization | Origin | How Removed | How Prevented | Picture | Typical Sizes | Typical Levels |
| Neoprene | White Elastomer | Siever (Gaskets) | Not Applicable | Pre-Process Inspection, Preventative Maintenance |  | ≤1MM | NOT EXPECTED - LOW LEVEL |
| FEP | White Plastic | Process Hose Lining | 4-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance | N/A | ≤1MM | NOT EXPECTED - LOW LEVEL |
| Poly-propylene | Natural colored opaque, opaqueoff-white plastic | ML Return Tank, Process Piping, Screw Conveyor Hopper | 4-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤2MM | NOT EXPECTED - LOW LEVEL |
| Kynar | Translucent Natural Plastic | Hot Tank Temperature Probe | Not Applicable | Pre-Process Inspection, Preventative Maintenance |  | ≤2MM | NOT EXPECTED - LOW LEVEL |

| Originating from the S04 Manufacturing Process Suite | | | | | | | |
|--|--|---|--|--|---|---------------|--------------------------|
| Identity | Characterization | Origin | How Removed | How Prevented | Picture | Typical Sizes | Typical Levels |
| PVC | White, Clear, Opaque plastic | ML Tote Process hose (Fittings), Centrifuge ML Return Hose, Dryer Exhaust Duct, Process Piping, Screw Conveyor Hose Centrifuge Wash Tank Piping | 4-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤2MM | NOT EXPECTED - LOW LEVEL |
| Silicone | Clear plastic, Orange elastomer fragment | Piping Gaskets, Dryer Bed Gaskets | Inspection of the Product, Reprocessing, 4-step Purification | Pre-Process Inspection, Preventative Maintenance |  | ≤1MM | NOT EXPECTED - LOW LEVEL |





Originating from the S04 Manufacturing Process Suite

| Identity | Characterization | Origin | How Removed | How Prevented | Picture | Typical Sizes | Typical Levels |
|---------------------|------------------|--|--|--|---|---------------|--------------------------|
| Stainless Steel 316 | Metallic shaving | Screw Conveyor, Hopper, Agitator (Body of Unit) Portable Sprayer (Vessel) Filter Housing Piping Tank Agitators (Body of Unit) UREA Wash Tank (Vessel) Centrifugal Pump (Housing) Centrifuge (Body of Unit) Fluid Bed Dryer (Body of Unit) Hot/Cold Tanks (Vessel) | 4-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤0.05MM | NOT EXPECTED - LOW LEVEL |
| Stainless Steel 304 | Metallic shaving | Siever | Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤0.05MM | NOT EXPECTED - LOW LEVEL |
| Tygon | Clear Elastomer | ML Pump Tubing | 4 Step Purification, | Pre-Process Inspection, Preventative Maintenance |  | ≤1MM | NOT EXPECTED - LOW LEVEL |
| Poly-carbonate | Clear Plastic | Screw Conveyor Sight Glass, Dryer Sight Glass, Cyclone | 4-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance | Not Available | ≤2MM | NOT EXPECTED - LOW LEVEL |
| HDPE | White HDPE | Centrifuge Sight Glass, Funnel Filter, Screw Conveyor | 4-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |  | ≤2MM | NOT EXPECTED - LOW LEVEL |
| CPVC | Gray Plastic | Filter Housing Piping | 4 Step Purification | Pre-Process Inspection, Preventative Maintenance |  | ≤2MM | 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 materials | | | | | |
|--|------------------|--------------------------------|--------------|---------------------------|---|
| Identity | Characterization | Origin | How Removed | How Prevented | Picture |
| Hexene LLDPE | Clear plastic | Poly Liner | Reprocessing | Inspection at time of use |  |
| Tyvek | White Plastic | Tyvek Liner | Reprocessing | Inspection at time of use |  |
| HDPE | White Plastic | Bottle (Packaging) | Reprocessing | Inspection at time of use |  |
| Polypropylene | Blue Plastic | Tamper Evident lid (Packaging) | Reprocessing | Inspection at time of use |  |

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 materials | | | | | |
|--|------------------|------------------|--------------|---------------------------|---|
| Identity | Characterization | Origin | How Removed | How Prevented | Picture |
| HMW-HDPE | Blue Plastic | Drum (Packaging) | Reprocessing | Inspection at time of use |  |

| Originating from the Packaging materials | | | | | |
|--|-----------------------|--|--------------|--|---|
| Identity | Characterization | Origin | How Removed | How Prevented | Picture |
| 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) | Reprocessing | Inspection at time of use |  |
| Cardboard | Brown | Pallet Liner | Reprocessing | Inspection at time of use |  |
| Wood | Wood Shaving | Pallet | Reprocessing | Inspection at time of use |  |