



100 Majestic Way, Bangor, PA 18013 / www.biospectra.us

TECHNICALLY UNAVOIDABLE PARTICLE PROFILE (TUPP) HEPES

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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 HEPES manufactured in process rooms at BioSpectra's Bangor, PA and Stroudsburg, PA facility.

2. SCOPE:

- 2.1. This TUPP applies to the manufacturing and packaging process of HEPES at BioSpectra's Bangor, PA and 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-0102, Degradation and Impurity Profiling SOP
- 3.8. BSI-SOP-0137, Discrepancy Investigation Procedure
- 3.9. BSI-SOP-0435, Equipment Qualification Master Plan
- 3.10. 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. 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 HEPES was approved as part of the validation of the HEPES manufacturing process.
- 4.4. 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.
- 4.5. 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.
- 4.6. 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.
- 4.7. 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.

4.8. Technically Unavoidable Particles (TUP):

- 4.8.1. 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.
- 4.8.2. Particles typically described as Technically Unavoidable Particles:
 - 4.8.2.1. A study should be initiated into the raw material, manufacturing and packaging processes to identify particles.
 - 4.8.2.1.1. Charred Particles:
 - 4.8.2.1.1.1. Discolored due to heat or friction.
 - 4.8.2.1.2. Materials of Construction (MOC):
 - 4.8.2.1.2.1. From manufacturing equipment that is product contacting or known to have normal and expected wear.
 - 4.8.2.1.2.2. From packaging components.
 - 4.8.2.1.2.3. Documented Risk Assessments for these are available in the associated FMEA and individual product TUPPs.
 - 4.8.2.1.3. Routinely used gaskets, seals, filters, etc.
 - 4.8.2.1.3.1. Expected to have normal wear.
 - 4.8.2.1.4. Lubricants, greases, oils or like materials.
 - 4.8.2.1.4.1. Discolored due to traces of such materials.
 - 4.8.2.1.4.2. Should be approved for use as Food grade or food contact grade or justified otherwise.
 - 4.8.2.1.5. Misshapen or morphologically distinct particles.
 - 4.8.2.1.6. Compressions/agglomerations, elongated/tangles or flakes.
 - 4.8.2.1.7. Color variation inherent of the product.
 - 4.8.2.1.7.1. Intrinsic components carried through from raw materials.
 - 4.8.2.1.7.2. 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:

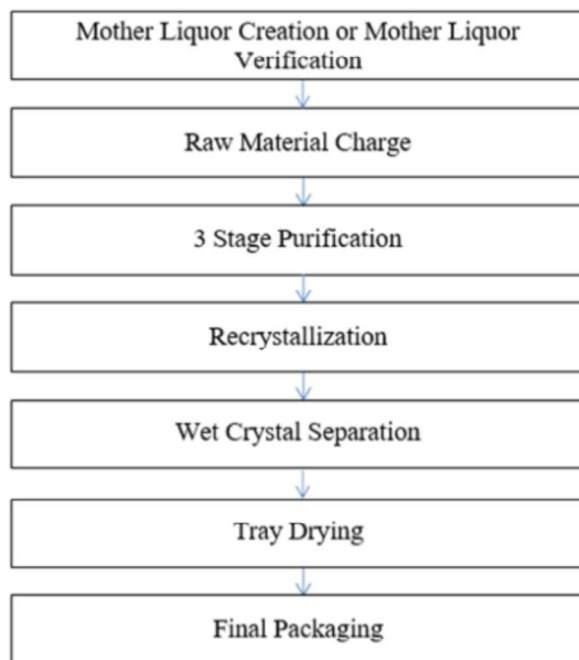


FIGURE 1. HEPES PROCESS FLOW DIAGRAM

7. PROFILE:

7.1. Manufacturing Locations:

7.1.1. Bangor, PA Majestic facility and Stroudsburg, PA Rockdale facility

7.2. Applicable Product Codes:

7.2.1. HEPE-3200 and below compliance grades

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

TABLE 1: ORIGINATING FROM THE PROCESS EQUIPMENT
Process Room N02 - Bangor

Identity	Characterization	Origin	How Removed	How Prevented	Picture
Glass	Glass Fragments	Process Tank 1 & Agitator Process Tank 2 & Agitator	Purification Inspection	Pre-Process Room Inspection Preventative Maintenance	Not Applicable
PTFE	Opaque White Plastic	Process Tank 1 Process Tank 2	Purification Inspection	Pre-Process Room Inspection Preventative Maintenance	
		Centrifugal Pump Centrifuge	Inspection		
Tantalum	Metallic Shavings	Process Tank 1 Process Tank 2	Purification Inspection	Pre-Process Room Inspection Preventative Maintenance	

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TABLE 1: ORIGINATING FROM THE PROCESS EQUIPMENT
Process Room N02 - Bangor

Identity	Characterization	Origin	How Removed	How Prevented	Picture
Polypropylene	Semi-opaque to off-white plastic	Process Tank 1 Process Tank 2	Purification Inspection	Pre-Process Room Inspection Preventative Maintenance	
Conductive Polypropylene	Natural colored Opaque off-white plastic	Diaphragm Pump	Inspection	Pre-Process Room Inspection Preventative Maintenance	
Santoprene	Off-white or yellow plastic	Diaphragm Pump	Inspection	Pre-Process Room Inspection Preventative Maintenance	
Hastelloy C-276	Metallic Shavings	Cartridge Filter Zeta Filter Polishing Filter	Inspection	Pre-Process Room Inspection Preventative Maintenance	
PVDF	Opaque Plastic, Black Plastic, Blue Plastic	Centrifugal Pump, Process Tanks, Portable Sprayer Nozzle	Inspection, Filtration	Pre-Process Room Inspection Preventative Maintenance	
Kalrez	Plastic	Centrifugal Pump	Inspection	Pre-Process Room Inspection Preventative Maintenance	
Alumina Ceramic	Ceramic Fragment	Centrifugal Pump	Inspection	Pre-Process Room Inspection Preventative Maintenance	
Halar	Polymer Lining	Centrifuge Liquid Seal Tank	Inspection	Pre-Process Room Inspection Preventative Maintenance	

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TABLE 1: ORIGINATING FROM THE PROCESS EQUIPMENT
Process Room N02 - Bangor

Identity	Characterization	Origin	How Removed	How Prevented	Picture
Hastelloy C22	Metallic Shavings	Centrifuge	Inspection	Pre-Process Room Inspection Preventative Maintenance	
HDPE	White Plastic	Mother Liquor Holding Tank Drying Trays	Inspection	Pre-Process Room Inspection Preventative Maintenance	
316 Stainless Steel	Metal Shaving	Tray Sifter	Inspection	Pre-Process Room Inspection Preventative Maintenance	
LLDPE	Clear Plastic	Sifting Bin	Inspection	Pre-Process Room Inspection Preventative Maintenance	
Polyethylene	Opaque White Plastic	Chemical Hoses	Inspection	Pre-Process Room Inspection	
PVC	White, Clear, or Gray Opaque Plastic	Milk Hoses	Inspection	Pre-Process Room Inspection	

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TABLE 2: ORIGINATING FROM THE PROCESS EQUIPMENT
Excipient Cell 1 Room E02 and Excipient Cell 2 Room E03 - Bangor

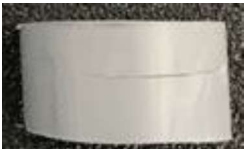
Identity	Characterization	Origin	How Removed	How Prevented	Picture
316 Stainless Steel	Metallic Shavings	Process Tanks Agitator Shaft/Blades Pilot Agitators Diaphragm Valves Process Piping Filter Housings Stokes Grinder	Purification Reprocessing	Pre-Process Room Inspection Preventative Maintenance	
304 Stainless Steel	Metallic Shavings	Stokes Grinder Hot and Cold Tank	Purification Reprocessing	Pre-Process Inspection Preventative Maintenance	
PTFE	Opaque White Plastic	Process Tanks Diaphragm Valves Piping Gaskets Filter O-rings	Purification Inspection	Pre-Process Room Inspection Preventative Maintenance	
Red FDA Silicone	Orange Elastomer Fragment	Process Tank Gaskets Pump Gaskets Filter O-ring	Purification Reprocessing	Pre-Process Room Inspection Preventative Maintenance	
Carbon	Black/Gray Fragments	Centrifugal Pump Carbon Seal Filters	Inspection Reprocessing	Pre-Process Room Inspection Preventative Maintenance	
Polypropylene	Natural colored Opaque off-white plastic	Diaphragm Pump Product Scoops Zeta Filter Nut	Inspection Reprocessing	Pre-Process Room Inspection Preventative Maintenance	

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TABLE 2: ORIGINATING FROM THE PROCESS EQUIPMENT
Excipient Cell 1 Room E02 and Excipient Cell 2 Room E03 - Bangor

Identity	Characterization	Origin	How Removed	How Prevented	Picture
USP Class VI Silicone	Clear Elastomer	Filter O-rings Sanitary Piping Gaskets	Inspection Reprocessing	Pre-Process Room Inspection Preventative Maintenance	
Silicon Carbide	Ceramic Fragments	Centrifugal Pump Stationary Seat	Reprocessing	Pre-Process Room Inspection Preventative Maintenance	
Hexene LLDPE	Clear Plastic	Liners	Inspection	Inspection at time of use	
HDPE	White	Funnel Filter Support Structure	Inspection Reprocessing	Pre-Process Inspection Preventative Maintenance	
CPVC	Gray Plastic	Funnel Filter Fittings	Inspection Reprocessing	Pre-Process Inspection Preventative Maintenance	

TABLE 3: ORIGINATING FROM THE PROCESS EQUIPMENT
Process Room 2 - Stroudsburg

Identity	Characterization	Origin	How Removed	How Prevented	Picture
CPVC	Gray Plastic	Funnel Filter Fittings	Inspection Reprocessing	Pre-Process Inspection Preventative Maintenance	

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TABLE 3: ORIGINATING FROM THE PROCESS EQUIPMENT
Process Room 2 - Stroudsburg

Identity	Characterization	Origin	How Removed	How Prevented	Picture
316 Stainless Steel	Metallic Shavings	Portable Sprayer Piping Agitator Shaft/Blades Tray Sifter Filter Housings Stokes Grinder	Purification Reprocessing	Pre-Process Room Inspection Preventative Maintenance	
304 Stainless Steel	Metallic Shavings	Stokes Grinder Hot and Cold Tank	Purification Reprocessing	Pre-Process Inspection Preventative Maintenance	
Silicon Carbide	Ceramic Fragments	Centrifugal Pump Stationary Seat	Reprocessing	Pre-Process Room Inspection Preventative Maintenance	
PTFE	Opaque White Plastic	Diaphragm Valves Piping Gaskets Sanitary Gasket Seals	Purification Inspection	Pre-Process Room Inspection Preventative Maintenance	
Carbon	Black/Gray Fragments	Centrifugal Pump Carbon Seal Filters	Inspection Reprocessing	Pre-Process Room Inspection Preventative Maintenance	
HDPE	White	Funnel Filter Support Structure	Inspection Reprocessing	Pre-Process Inspection Preventative Maintenance	
Polypropylene	Natural colored Opaque off-white plastic	Funnel Filter (Cloth) Diaphragm Pump Body	Inspection	Pre-Process Room Inspection Preventative Maintenance	
Cellulose	Fiber	Filter Media	Purification Reprocessing	Pre-Process Room Inspection Replacement of Filters	

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TABLE 3: ORIGINATING FROM THE PROCESS EQUIPMENT
Process Room 2 - Stroudsburg

Identity	Characterization	Origin	How Removed	How Prevented	Picture
Silica	White Powder	Filter Media	Purification Reprocessing	Pre-Process Room Inspection Replacement of Filters	
Polyethersulfone	Light amber Transparent	Filter Media	Inspection	Pre-Process Room Inspection	Not Applicable
PVC	White, Clear, or Gray Opaque Plastic	Hoses	Inspection	Pre-Process Room Inspection	
Viton	Black Elastomer	Gaskets Tank Discharge Valves	Purification Inspection	Pre-Process Room Inspection	
Platinum Cured Silicon	Clear Plastic Orange Elastomer Fragment	Gaskets	Purification Inspection	Pre-Process Room Inspection	
U.H.M.W. PE	Clear Plastic	Chemical Hose	Purification Inspection	Pre-Process Room Inspection	

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

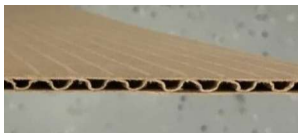
7.4.1. The following TUPPs are dependent on the packaging type.

TABLE 4: ORIGINATING FROM THE PACKAGING COMPONENTS					
Identity	Characterization	Origin	How Removed	How Prevented	Picture
LLDPE	Clear Plastic	Liner (Packaging)	Inspection at time of use	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	

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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 5: 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 and Product Care procedure	
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 and Product Care Procedure	
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	
BSI Plastic	Blue, Green, or Gray Plastic	Pallet	Inspection at time of use	Inspection at time of use	

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