



TECHNICALLY UNAVOIDABLE PARTICLE PROFILE (TUPP) – HEPES BIO EXCIPIENT

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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 Room 2 at BioSpectra's Stroudsburg, PA facility.

2. SCOPE:

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

3. REFERENCES:

- 3.1. [Change Control](#)
- 3.2. [Contaminant Form](#)
- 3.3. [Degradation and Impurity Profiling SOP](#)
- 3.4. [Discrepancy Investigation Procedure](#)
- 3.5. [Equipment Preventative Maintenance](#)
- 3.6. [Equipment Qualification Master Plan](#)
- 3.7. [FMEA & CE Matrix Template](#)
- 3.8. [IPEC Technically Unavoidable Particle Profile \(TUPP\) Guide](#)
- 3.9. [Pre-Process Room Inspection SOP](#)
- 3.10. [Supplier Corrective Action Request](#)
- 3.11. [Written and Verbal Complaints](#)

4. DEFINITIONS:

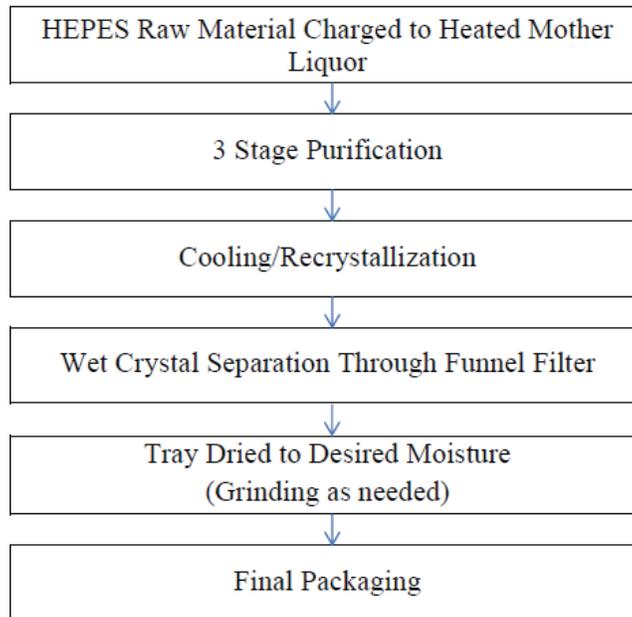
- 4.1. Atypical Particle: A visibly different particle that can be viewed with the naked eye, that is not consistent with a Technically Unavoidable Particle Profile (TUPP).
- 4.2. Contaminant: A visibly different particle that is not inherent of the process or is considered to be avoidable.
- 4.3. Technically 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 Bangor, 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 Bangor, 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.
 - 4.7.2.1.5.1. Compressions/agglomerations, elongated/tangles or flakes.
 - 4.7.2.1.6. Color variation inherent of the product.
 - 4.7.2.1.7. Intrinsic components carried through from raw materials.
 - 4.7.2.1.7.1. 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

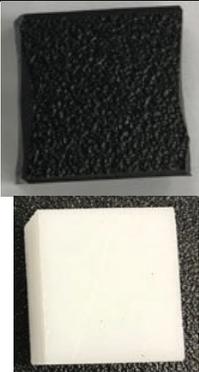
7.2. Applicable Product Codes:

7.2.1. HEPE-3200 AND BELOW COMPLIANCE GRADES

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

Originating from the Manufacturing process							
Identity	Characterization	Origin	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
CPVC	Gray Plastic	Funnel Filter (Pipe Fittings)	Inspection of the product	Pre-Process Inspection		≤2mm	Not Expected – Low Level
316 Stainless Steel	Metallic Shaving	Portable Sprayer (Vessel and spray nozzle) Polishing Filter (Housing) Piping Tank Agitators (Body of Unit) Centrifugal Pump (Housing) Tray Sifter (Body of Unit) Stokes Grinder (Body of Unit) Funnel Filter (Fasteners and Fittings)	3 Step Purification, Inspection of the product	Pre-Process Inspection		≤0.5mm	Not Expected – Low Level
304 Stainless Steel	Metallic Shaving	Hot Tank (Body of Unit) Cold Tank (Body of Unit) Stokes Grinder (Body of Unit)	3 Step Purification, Inspection of the product	Pre-Process Inspection		≤0.5mm	Not Expected – Low Level
Silicon Carbide	Ceramic Fragment	Centrifugal Pump Stationary Seat	Reprocessing	Pre-Process Inspection, Preventative Maintenance		≤0.5mm	Not Expected – Low Level

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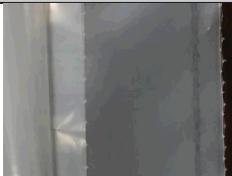
Originating from the Manufacturing process							
Identity	Characterization	Origin	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
							
PTFE	Opaque White Plastic	Diaphragm Pump (Balls) Sanitary Gaskets Seals	3 Step Purification, Inspection of the product	Pre-Process Inspection		≤2mm	Not Expected – Low Level
Carbon	Black or Gray Fragments	Centrifugal Pump (Pump seals), Filtration Media	Inspection of the product	Pre-Process Inspection		≤0.5mm	Not Expected – Low Level
HDPE	Plastic	Funnel Filter (Internal Supports)	Inspection of the product	Pre-Process Inspection		≤2mm	Not Expected – Low Level
Polypropylene	Natural Colored Opaque Off-White, Blue Plastic	Funnel Filter (Cloth) Diaphragm Pump (Body of Unit), Filtration Media	Inspection of the product	Pre-Process Inspection		≤2mm	Not Expected – Low Level
Cellulose	Fiber	Filtration (Filter media)	3-Step Purification, Reprocessing	Replacement of Filters, Inspection		≤0.5mm	Not Expected – Low Level
Silica	White Powder	Filtration (Filter media)	3-Step Purification, Reprocessing	Replacement of Filters, Inspection		≤0.5mm	Not Expected – Low Level

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Originating from the Manufacturing process							
Identity	Characterization	Origin	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
Polyethersulfone	Unavailable	Filtration (Filter media)	Inspection of the product	Pre-Process Inspection	Picture Unavailable	≤0.5mm	Not Expected – Low Level
PVC	White, Clear, Opaque Plastic	Hoses	3 Step Purification, Inspection of the product	Pre-Process Inspection		≤2mm	Not Expected – Low Level
Viton	Black Elastomer	Gaskets, Tank Discharge Valves	3 Step Purification, Inspection of the product	Pre-Process Inspection		≤1mm	Not Expected – Low Level
Platinum Cured Silicon	Clear Plastic, Orange Elastomer Fragment	Gaskets	3 Step Purification, Inspection of the product	Pre-Process Inspection		≤1mm	Not Expected – Low Level
U.H.M.W. PE	Clear Plastic	Chemical Hose	3 Step Purification, Inspection of the product	Pre-Process Inspection		≤2mm	Not Expected – Low Level

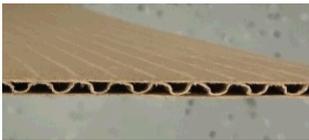
7.4. TUPPs originating from product contacting surfaces of the packaging components:

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

Originating from the Packaging materials							
Identity	Characterization	Origin	How Removed	How Prevented	Picture	Typical Sizes	Typical Levels
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.

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	
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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TECHNICALLY UNAVOIDABLE PARTICLE PROFILE (TUPP) – HEPES

EXCIPIENT CELL 1 ROOM E02
AND
EXCIPIENT CELL 2 ROOM E03

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 Excipient Cell 1 Room E02 and Excipient Cell 2 Room E03 at BioSpectra's Bangor, PA facility used in the manufacture of cGMP HEPES Bio Excipient and Bio Pharma grades.

2. SCOPE:

- 2.1. This TUPP applies to the manufacturing and packaging process of HEPES manufactured at BioSpectra's Bangor, PA facility in Excipient Cell 1 Room E02 or Excipient Cell 2 Room E03.

3. REFERENCES:

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

4. DEFINITIONS:

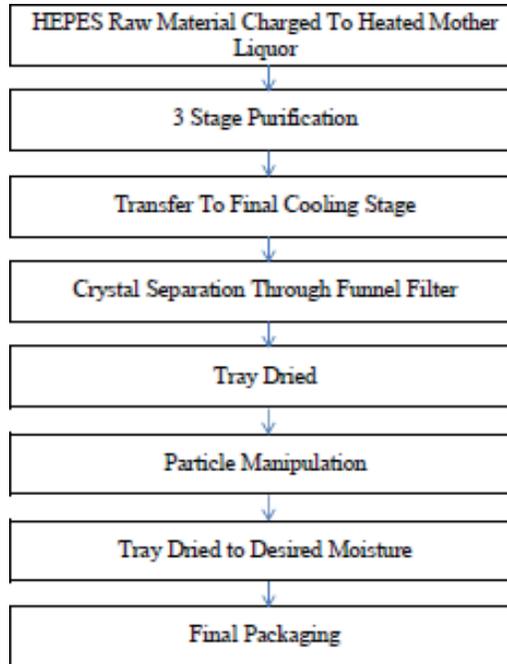
- 4.1. Technically Unavoidable Particle (TUP): A visibly different particle that can be viewed with the naked eye that is inherent to the raw material, manufacturing process or product and does not pose risk to patient safety.
- 4.2. Technically Unavoidable Particle Profiles (TUPPs): A report on all 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 HEPES was approved as part of the validation of the HEPES 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:

cGMP HEPES Manufacturing Process Flow Diagram



7. PROFILE:

7.1. Manufacturing Location:

7.1.1. Bangor, PA Facility

7.2. Applicable Product Codes:

7.2.1. HE3XXX and HE4XXX compliance grades

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

Originating from the Manufacturing process					
Identity	Characterization	Origin	How Removed	How Prevented	Picture (Example of Source)
316 Stainless Steel	Metallic Shaving	Process Tanks Agitator Shaft/Blades Pilot Agitators Diaphragm Valves Process Piping Filter Housings	Purification, Reprocessing	Pre-Process Inspection, Preventative Maintenance	
		Centrifugal Pump Head and Impeller Diaphragm Pump Fittings Tray Sifter	Reprocessing		
PTFE	Opaque White Plastic	Process Tank Gaskets Process Tank Diaphragm Valves Sanitary Piping Gaskets Process Piping Valve Diaphragms Diaphragm Pump Diaphragm Diaphragm Pump Check Valve Balls Filter O-ring	Purification, Reprocessing	Pre-Process Inspection, Preventative Maintenance	
Red FDA Silicone	Orange elastomer Fragment	Process Tank Gaskets Diaphragm Pump Gaskets Filter O-Ring	Purification, Reprocessing	Pre-Process Inspection, Preventative Maintenance	
Carbon	Black or Gray Fragments	Centrifugal Pump Rotating Carbon Seal Filter	Reprocessing	Pre-Process Inspection, Preventative Maintenance	Not Available

Originating from the Manufacturing process					
Identity	Characterization	Origin	How Removed	How Prevented	Picture (Example of Source)
Polypropylene	Natural Colored Opaque Off-White, Blue Plastic	Diaphragm Pump Fittings Diaphragm Pump Fluid Covers Diaphragm Pump Manifolds Diaphragm Pump Check Valve Seats Product Scoops Zeta Filter Nut	Reprocessing	Pre-Process Inspection, Preventative Maintenance	
USP Class VI Silicone	Clear Elastomer	Filter O-rings Sanitary Piping Gaskets	Reprocessing	Pre-Process Inspection, Preventative Maintenance	
Silicon Carbide	Ceramic Fragment	Centrifugal Pump Stationary seat	Reprocessing	Pre-Process Inspection, Preventative Maintenance	
Hexene LLDPE	Clear plastic	Liners	Reprocessing	Inspection at the time of use	

Originating from the Manufacturing process- Mobile Equipment					
Identity	Characterization	Origin	How Removed	How Prevented	Picture (Example of Source)
316 Stainless Steel	Metallic Shaving	Funnel Filter Fittings Stokes Grinder	Reprocessing	Pre-Process Inspection, Preventative Maintenance	
304 Stainless Steel	Metallic Shaving	Stokes Grinder	Reprocessing	Pre-Process Inspection, Preventative Maintenance	

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Polypropylene	Natural Colored Opaque Off- White, Blue Plastic	Funnel Filter Shell Funnel Filter Perforated plate Filter Cloth	Reprocessing	Pre-Process Inspection, Preventative Maintenance	
HDPE	White HDPE	Funnel Filter Support structure Drying Trays	Reprocessing	Pre-Process Inspection, Preventative Maintenance	
CPVC	Gray Plastic	Funnel Filter Fittings	Reprocessing	Pre-Process Inspection, Preventative Maintenance	

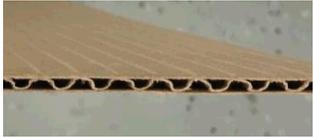
7.4. TUPPs originating from product contacting surfaces of the packaging components:

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 (Example of Source)
Hexene LLDPE	Clear Plastic	Liner (Packaging)	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.

Atypical particles: originating from the packaging components					
Identity	Characterization	Origin	How Removed	How Prevented	Picture (Example of Source)
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)	Reprocessing	Inspection at time of use and Product Care Procedure	
Cardboard	Brown	Pallet Liner	Reprocessing	Inspection at time of use and Product Care Procedure	
Wood	Wood Shaving	Pallet	Reprocessing	Inspection at time of use and Product Care Procedure	