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## TECHNICALLY UNAVOIDABLE PARTICLE PROFILE (TUPP) – UREA

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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 Urea manufactured in Process Suite 4 at BioSpectra's Stroudsburg, PA manufacturing facility.

## 2. SCOPE:

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

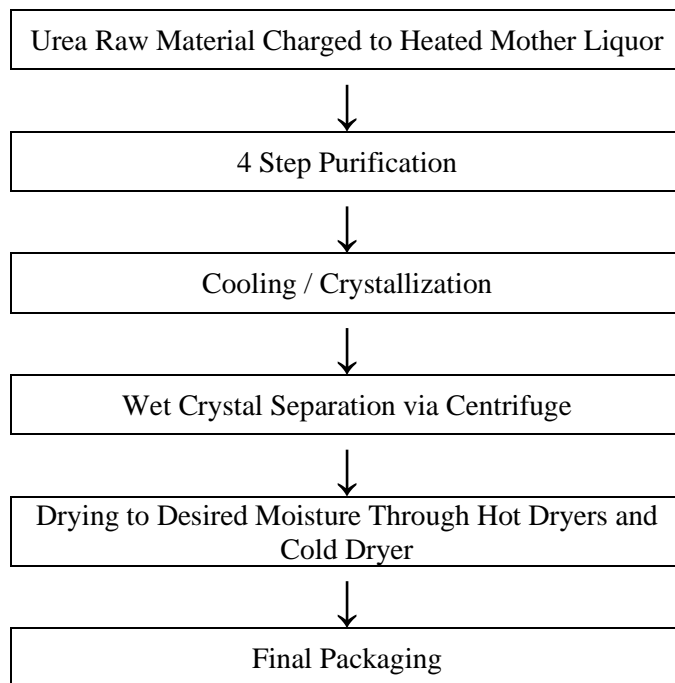
## 4. DEFINITIONS:

- 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 report 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.
    - 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 4 at BioSpectra's Stroudsburg, PA manufacturing facility





### 7.2. Applicable Product Codes:


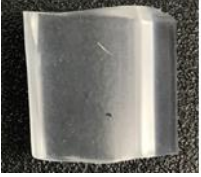



7.2.1. All Urea excipient and below product codes

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

**Table 1: Originating from the S04 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<br>- Low Level |
| Silica          | White Powder             | Filtration (Filter media)  | 4-Step Purification, Reprocessing                            | Replacement of Filters, Inspection                                       |    | ≤1MM          | Not Expected<br>- 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<br>- 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<br>- Low Level |
| Silicon Carbide | Ceramic Fragment         | Centrifugal Pump Stationary Seat   | 4-Step Purification, Reprocessing                            | Pre-Process Inspection, Preventative Maintenance                         |  | ≤0.05MM       | Not Expected<br>- 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<br>- Low Level |
| Neoprene        | White Elastomer          | Siever (Gaskets)   | Not Applicable   | Pre-Process Inspection, Preventative Maintenance                         |  | ≤1MM          | Not Expected<br>- Low Level |


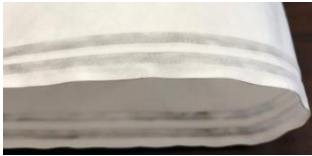

| Identity            | Characterization                                 | Origin   | How Removed  | How Prevented                                    | Picture   | Typical Sizes | Typical Levels           |
|---------------------|--|--|--|--|---|---------------|--------------------------|
| FEP                 | White Plastic                                    | Process Hose Lining  | 4-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance | Not Applicable  | ≤1MM          | Not Expected - Low Level |
| Poly-propylene      | Natural colored opaque, opaque off-white plastic | ML Return Tank, Process Piping, Vacuum Conveyor Hopper   | 4-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 Hose, Dryer Exhaust Duct, Process Piping, Vacuum 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 polymer, 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 |
| Stainless Steel 316 | Metallic shaving                                 | Vacuum Conveyor, Hopper, Agitator (Body of Unit), Portable Sprayer (Vessel), Filter Housing, Piping, Tank Agitators (Body of Unit), 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 |

| Identity            | Characterization | Origin   | How Removed  | How Prevented                                    | Picture   | Typical Sizes | Typical Levels              |
|---------------------|------------------|--|--|--|---|---------------|-----------------------------|
| Stainless Steel 304 | Metallic shaving | Siever   | Inspection of the Product, Reprocessing                      | Pre-Process Inspection, Preventative Maintenance |    | ≤0.05MM       | Not Expected<br>- Low Level |
| Tygon               | Clear Elastomer  | ML Pump Tubing                                   | 4 Step Purification  | Pre-Process Inspection, Preventative Maintenance |    | ≤1MM          | Not Expected<br>- Low Level |
| Poly-carbonate      | Clear Plastic    | Piping Sight Glass, Dryer Sight Glass, Cyclone   | 4-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance | Not Available   | ≤2MM          | Not Expected<br>- Low Level |
| HDPE                | White HDPE       | Centrifuge flange spacer, Vacuum Conveyor Hopper | 4-Step Purification, Inspection of the Product, Reprocessing | Pre-Process Inspection, Preventative Maintenance |    | ≤2MM          | Not Expected<br>- Low Level |
| CPVC                | Gray Plastic     | Filter Housing Piping                            | 4 Step Purification  | Pre-Process Inspection, Preventative Maintenance |  | ≤2MM          | Not Expected<br>- Low Level |
| Vinyl plastic       | Blue             | Sanitary fitting cover                           | Inspection at time of use                                    | Inspection at time of use                        |  | ≤2MM          | Not Expected<br>- 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.




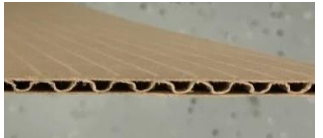

**Table 2: Originating from product contacting surfaces of the packaging components**

| 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 and 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.

**Table 3: Originating from non-product contacting surfaces of the packaging**

| 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)<br>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                            |  |

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 |