STRATEGIES FOR THE CONTROL OF VISIBLE PARTICLES FOR MANUFACTURING STERILE DEVICES

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Presentation Outline: Strategies for the Control of Visible Particles for Manufacturing Sterile Devices

1. Background of Visible Particles
2. Sources and Risk of Visible Particles
3. Points to Consider for Quality Risk Management
4. Detection of Visible Particles
5. Strategies for Effective Control of Visible Particles
6. Conclusions
7. Q/A session
8. Interactive Exercise
Definition of Visible Particles

- Visible Particles are defined as those particles that can be detected under controlled conditions by the unaided human eye (without supplemental magnification).
- In general, particles can be categorized based on their sizes.

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<tr>
<th>Sub-micron</th>
<th>Sub-visible</th>
<th>Visible</th>
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<tr>
<td>100 - 1000nm</td>
<td>1 - 100 μm</td>
<td>&gt; 100 μm</td>
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- They can be characterized depending on their source, type, size and chemical composition.
Particles can be Classified in to Two Categories - Extrinsic and Intrinsic

- **Extrinsic Particles** are not emanated by processing conditions and/or subassembly/assembly processes and are foreign and unexpected in the final devices or product. Examples of the Extrinsic Particle include cellulose fibers, clothing fragments, skin flakes, glass, hair, plastic, metals, paint.

- **Extrinsic Particles** present a great risk to sterility assurance for sterile devices.

- **Intrinsic Particles** are those particle that originate from packaging materials, subassembly/assembly processes, or processing conditions.
Visible Particles can Cause Serious Adverse Reaction and Affect the Implantable Devices Quality

• The presence of Visible Particle in the implantable/sterile devices can affect the proper functionality of the device

• Significant particulate and/or fiber contamination that comes in contact with blood or CSF can potentially cause blockage of blood vessels, thrombosis or other serious adverse reactions

• Fibrous contamination can damage the valves in the venous system which can cause painful conditions and edema

• Visible Particle pose greater risk to sterility assurance as their bioburden contents remain unknown and uncontrolled

• Visible Particle contamination increases the risk of process control failure and product contamination due to particles tracking and dispersion
Points to Consider for the Assessment and Management of Quality Risk for Visible Particles

• Identification and composition of the Visible Particle is the first step in characterizing the particle risk

• Based on objective data, the frequency at which the Visible Particle contamination is likely to occur should be determined

• Presence of particles i.e. single particle or multiple particles in a single device unit

• Types of particles i.e. single type particle or multiple types Visible Particles in a single device unit/multiple devices

• Distribution of Visible Particles whether isolated event or their detection in several units of the same batch
continued: Points to Consider for the Assessment and Management of Quality Risk for Visible Particles

• Dissemination of the Visible Particles to other processes or product manufactured in the same room or other rooms

• Determination of frequency (how often) of Visible Particles hazard likely to occur within a lot or across several product lots

• Determination of frequency (how often) of Visible Particles hazard likely to occur within a lot or across different product lot/lots

• Size/extent of the hazard (how wide is the spread of the hazard, same facility or multiple facilities

• Determine leading or lagging trends of the hazard
continued: Points to Consider for the Assessment and Management of Quality Risk for Visible Particles

• Determine failure rates by reviewing source documents
  o Complaint Data (Trends and Spike)
  o Exception Reports/Deviations/OOS
  o CAPA Records
  o Manufacturing Batch Records
  o Supplier Incoming Reports/Data
  o Inspection Results of Inventory and Retain Samples

• Determine potential causes of the hazard and determine how long these causes have been occurring

• Understand the leading and lagging trend. Estimate the base level of occurrences within the affected product lots and other products
continued: Points to Consider for the Assessment and Management of Quality Risk for Visible Particles

• Assess the sub-assembling, assembling and manufacturing processes where particles are generated, detected and removed

• Identify the processes that generate particles and categorize the processes according to the extent of particle generation

• Understand what type of Extrinsic and Intrinsic particles are generated

• Assess the personnel activities and particle shedding processes

• Identify and categorize the causes of particle generation e.g. low, medium and high categories
Strategies and Approaches for the Effective Control of Visible Particle Contamination

• Identify the effective means of detection of Intrinsic and Extrinsic sources of Visible Particles and generating processes

• Identify type and composition of the recovered Visible Particle

• Develop methods to prevent and restrict ingress of new Visible Particles in the manufacturing environment

• Eliminate or minimize the accumulation of Visible Particles in the manufacturing environment

• Prevent generation of new Visible Particle contamination within the manufacturing process and environment

• Prevent Visible Particle dispersion and transfer to other processes and locations in the manufacturing area
Detection of Intrinsic and Extrinsic Sources of Visible Particles

• Routinely used equipment for environmental nonviable particulate monitoring cannot detect Visible Particles greater than 20µm

• The settling of the nonviable particles depends on their particle size and settling velocities

• Witness plates or equivalent device can be used to assess the fallout contamination levels of particles ≥ 60 µm

• To improve recovery of particles on witness plates, it is necessary to optimize the exposure time to clean room environment

• The particles recovered on witness plates can be characterized to determine the quantity, types, size, shape, texture, and chemical nature
Development of Corrective and Preventive Action Plan

- Characteristics of captured particles provide opportunities to conduct root-cause-analysis to identify the processes materials used and operations that generate specific particles.

- Depending on the findings, an appropriate corrective and preventive action plan can be developed to minimize the generation of specific particles from a processes.

- Such approaches can improve the manufacturing operation and operational practices.

- Such approaches prevent /minimize the risks of accumulation of particles, their dispersion, and restrict ingress of new particles.
Control of Visible Particles During the Manufacturing of Sterile Devices is Complex and Challenging

- Medical devices use variety of plastic components. Plastic materials are the major source of static charges.

- When these products are charged, they attract more particles to their surface.

- Static attraction is the major contributor of Visible Particle contamination and yield losses.

- Different device manufacturing processes are carried out by multiple operators in one large ISO 7/ISO 8 and in ISO6 areas.

- Upstream device component manufacturing process may consist of cutting, welding, grinding, sewing, ballooning, and kitting operations that generate significant amount of Visible Particles.
Implementation of Air Ionization Unit for Neutralization of Static Charges

• These devices neutralize the static properties and remove the particles adherent to clean room surfaces and device surfaces.

• Air Ionizers generate large quantities of positive and negative ions in the surrounding atmosphere and rapidly neutralize charged surfaces.

• As the emitted ions flow through the air, they are attracted to oppositely charged particles and surfaces and neutralize of charged surfaces.

• Based on the data from particle characterization studies, an Air Ionization Unit can be installed at appropriate locations.
Diagrammatic Representation of Generation of Static Charges and Their Neutralization by Ionization Units

Generation of static charges on plastic surfaces*

How Ionization units work

*Courtesy of SIMCO Ions
Contamination control solutions
Factors Affecting the Ionization Applications

• Factor affecting the Ionization System
  o Level of static charge
  o Ionizer discharge time based on the application
  o Balance of the ionizer
  o Area that needs to be ionized

• Ionizer discharge times are affected by
  o Distance from the target area
  o Air Flow that delivers the ions to the target
  o Air flow from the Ionizer to the target
  o Humidity

• Perform system characterization studies and validation
Minimize the Use of Particle Shedding Materials

- Minimize the use of particle shedding materials (for example, paper, plastic wrapping, aluminum foils, labeling tags, material used for wrapping the manufacturing goods for autoclaving, mop and wipes).

- During manufacturing operations and where possible be replaced with non-particle shedding materials.

- The wrapping materials be effectively cleanable and sanitizable to remove particles and bacteria.

- To minimize particle adherence during storage, Air Ionization Unit can be placed in the storage and material transfer rooms.
Raw Materials and Component Supplier Controls

• Plastic Materials should be considered as Critical Raw Material.

• Their handling should be control during the component manufacturing.

• Components storage containers-closure system should be made-up of static free material.

• Prior to storage they should be exposed to Ionization Units.

• Component storage conditions such as humidity and temperature should be validated.

• Storage area at the supplier site can be fitted with static neutralizing units.
Raw Materials and Component User Controls

- Visible Particle Control should be one of the major requirements for the vendor selection and qualification processes.

- Particulate cleanliness specifications and limits should be an important component of Quality Agreement.

- Robust Vendor Qualification and Disqualification Procedures.

- Good receiving and distribution and transfer processes are critical to prevent or minimize the risk of introducing new particles.

- Robust inspection of incoming goods, testing, monitoring, and data trending processes are essential.

- Materials should be packed in triple bags.
Technical Framework for Facility Design for Aseptic Processing

• Facility should have sufficient capacity to accommodate requirements of specific processes, equipment and number of personnel required to properly support manufacturing operations

• Cleanable clean room surfaces should be capable of withstanding the harsh chemicals treatment to prevent contaminants build-up

• Walls and floors finished should be smooth, non-porous, monolithic surface to prevent build-up of organisms and particles

• Acceptable walls and floors should be essentially seamless surfaces

• The ceilings should consist of well-sealed light fixtures and HEPA filtration system
Gowning Room Design

• Gowning Room should have the same classification as the area they serve

• The flow of material and personnel in the Gowning Rooms is unidirectional

• The operator and their clothing are statically charged which cause binding of large particles leading to particle accumulation

• The use of Ionization Systems in the Gowning Room significantly removes the particles from operator clothing to prevent particle transfer and build-up in the classified manufacturing areas

• Contamination load in the gowning area is very high and thus requires high air exchange rates to maintain ISO 14644 air quality and cleanliness requirements
Technical Framework for the Construction Material and Fabric Quality Used for Gowning Materials

- The construction material and fabric quality used for gowning materials should be certified to shed very low quantities of particles and fiber, retain microorganisms and control electrostatic discharge.

- Fabric should sustain repeated washing and sterilization without loss of performance.

- Fabric should be breathable lightweight material to promote wearer comfort and made-up of 100% or 99% polyester and 1% carbon.

- The fabric should be made-up of non-lining yarn material to reduce the risk of fiber generation and promotes static dissipation.
Technical Framework for the Construction Material and Fabric Quality Used for Gowning Materials

• The fabric should have high density construction to resist fluid, bacterial, and particle penetration

• The suitability of fabric for the microbial and particulate contamination control requires the following performance characteristics testing and implementing technical specifications:
  o Fabric pore size determination
  o Particle retention efficiency and dry linting propensity test
  o Water vapor permeability and air permeability for the wearer comfort
  o Electrostatic dissipation
  o Aberration resistance, and body box testing to establish the number of microbial and nonviable particles shed during actual use conditions
  o The number of wash and sterilization cycles should be qualified
Technical Framework for Gown Design

• The gowns are designed to ensure easy gowning, close fitting and seal the gaps around cuff, neck, hood, legs, and chest area (zipper)

• The other important components gowning include face mask and gloves

• Garments worn under the clean room gowns are usually non-particle shedding undergarment plant uniforms made of 100% polyester are recommended
Clean room Cleaning Processes: Preventive Cleaning and Active Cleaning

- The purpose of cleaning is to prevent their dispersion inside the clean room and remove the existing chemical residues, particles and microbial contaminants

- **Preventive Cleaning Process** is a proactive activity and is performed after rebuilding or construction activities
  - The purpose of preventive cleaning is to prevent entry/and dispersion of particles and microbial contaminants inside the clean room.
  - This process consists of dry cleaning, wet cleaning/sanitization process

- **Active Cleaning** removes existing particles, solid material and liquids materials from the clean room and equipment surfaces
  - When used in combination with biocidal agents, significantly reduce surface bioburden
Cleaning Methods: Dry Cleaning and Wet Cleaning

- For device manufacturing a combination of both dry and wet methods are recommended

- **Dry Cleaning Method**
  - It is the first step in cleaning process, typically used prior to Wet Cleaning Process
  - The HEPA vacuum cleaning is the most commonly used method
  - Dry Cleaning Method is routinely used in preventive and active cleaning processes
  - Clean room compatible vacuum cleaners equipped with HEPA filters are 100% effective in removing particle size approaching 100µm
  - Vacuum cleaners are poorly effective in removing ≤10 µm particles
  - All accessible surfaces are vacuumed from the cleanest part of the room to the dirtiest part of the room
continued Cleaning Methods: Wet Cleaning Method

• Wet Cleaning method uses 0.2 filter sterilized cleaning solutions that contain detergents and surface tension reducing agents to facilitate the particle/chemical residues removal

• Wet Cleaning process, consisting of mopping and wiping of all clean room surfaces with an approved cleaning solution

• The sterile cleaning tools, cleaning supplies such as particulate free wipes, mops, and equipment are single used

• For Wet Cleaning process typically uses autoclavable stainless steel or plastic buckets and two or three bucket mop system
Key Cleaning Process Parameters

• Frequency of rinsing the mop in WFI after few application of cleaning solutions

• The length of use of mops prior to rinsing and wetting with more cleaning solution should be defined

• Frequency of changing wipe

• Frequency of changing sterile water for injection (WFI) in the buckets
Critical Components of Cleaning Process

• Effective Operator Facility Cleaning Training Program

• Such Training Program should include initial operator qualification, operator proficiency assessments

• Cleaning operator qualification and disqualification

• Cleaning solution preparations

• Is the critical component of facility contamination control program

• Periodic audits by QA to assure that operators maintain their qualified status
Facility Cleaning Surveillance Program

• A Facility Cleaning Surveillance Program is an effective tool to assure continuous verification of the effectiveness of facility cleaning.

• This Program entails periodic visual observation of the clean room surfaces; facility corrosion, and rouging of stainless steel surface and equipment.

• Chemical analysis can be performed to determine the build-up disinfectant and product residues.

• Periodic visual inspection of clean room surface can be performed using appropriate light source, sampling on wipes, mop and microscopic examination and swabs followed by chemical extraction methodologies and relevant testing.
Conclusions

• Facility Design should meet the requirements of walls floors and ceiling finish and specific processes to be conducted

• Comprehensive characterization of sources, types of particles and implementing neutralization of static charges are crucial for an effective Visible Particle Control Program

• Installing Ionization Systems in appropriate manufacturing, storage and product transfer areas can significantly reduce the Visible Particle accumulation and yield losses

• The fabric quality of clean room protective garments and their correct donning process offer effective control of Visible Particles

• The Dry and Wet Cleaning processes and Facility Surveillance Program are crucial for the effective particle removal process
THANK YOU