Visible Particles in Injectables - the Awesome Power of Facility Material Libraries

Abstract:

This paper explores the **critical role of facility material libraries in the sterile manufacturing of injectable drugs**, acknowledging that the presence of visible particles in these drugs, while undesirable, is an unavoidable reality. **Building a facility particle library provides the foundation for effective particle control and establishes a risk-based approach to quality management**. By establishing a library, manufacturers define a "normal" level of particles within their facility, enabling them to quickly identify any deviation from this baseline. This approach **offers numerous benefits, including faster and more streamlined investigations**. With a clear understanding of expected particle levels, investigations can swiftly focus on critical events, leading to more efficient deviation management. Ultimately, this leads to improved overall quality management and enhanced patient safety. Additionally, **implementing a facility particle library increases operational efficiency, which translates into cost savings**.

Facility particle libraries are also vital for supporting continuous improvement programs in sterile manufacturing, especially for facilities involved in cell and gene therapy product manufacturing. The unique challenges posed by the diverse single-use components in this field underscore the importance of high-quality, facility-specific particle libraries for accurate particle identification. This level of accuracy is often not achievable with publicly available spectral libraries. The paper concludes that **facility particle libraries are a valuable investment for sterile drug manufacturers, contributing to high-quality products and operational excellence**.

Visible particles - cutting through regulatory complexity

Visible particles - a definition?

The current compendial and regulatory guidance documents relevant to “visible particles” provide an implicit definition for this term, as particles that are readily detectable by the naked human eye when using standardized inspection conditions (light intensity, duration, background). These guidance documents also acknowledge the probabilistic nature of visible particle detection, which is the main reason for the lack of fixed size thresholds of particle detectability and for the use of statistical definitions of detectability - via threshold studies, or Knapp tests - instead.

Assessing Particle risk

There are different routes of ingress and pathways of formation of particles in the drug product - each implying different risk - which is why it is helpful to categorize and classify particles according to their origin and nature. Currently, the main pharmacopoeial chapters that provide guidance with regard to the types of particles related to risk are the advisory (informational) chapters USP<1790> and EP 5.17.2.. These two chapters differ slightly in their approach in defining the particle categories:

USP <1790> defines three particle categories:

- **extrinsic** ("foreign to the manufacturing process", "non-process related")
- **intrinsic** ("from within the process", "process-related")
- **inherent** ("dosage-form-related")

EP 5.17.2. - defines only two categories:

- **extrinsic** ("deriving from the environment, equipment, primary packaging or personnel") - roughly corresponding to the sum of "extrinsic" and "intrinsic" categories defined by USP

- **intrinsic** ("related to the formulation, including active substances and excipients, process residuals or contaminants, or resulting from interactions between the formulation and primary packaging") - roughly corresponding to the "inherent" category defined by USP

Some consider the more granular approach by the USP more helpful, as it gives the opportunity to differentiate between particle extrinsic to the process and the facility (i.e. which occurrences may indicate potential GMP or process breach - HIGH RISK) and particles from within the process (i.e. which occurrences cannot be completely avoided during normal operations - MODERATE TO LOW RISK). Although the presence of all visible particles in injectable products is undesired (apart from some exceptions intentionally present, as mentioned by both the USP and EP), such category differentiation is practical and helpful, as it may be easily reflected in internal standard operating procedures (SOPs), detailing the workflows for characterization, risk assessments and quality decisions related to particles.

In assessments of the risk related to particle ingress in injectable drug products in the context of sterile manufacturing, there are two aspects that are important to consider:

- **Safety risk** (risk for the patients)
- Risk related to **potential loss of process control**

With regard to the former, the typical factors in focus of the assessment are the nature of the particle and its attributes, the route (and frequency) of administration and the characteristics of the intended patient population (J Ayres 2018: https://pubmed.ncbi.nlm.nih.gov/30158238/). The latter requires evaluation of the frequency of occurrence of the given type of particle, but also - evaluation of the nature and source of the particle (BPOG 2021: https://www.biophorum.com/download/standardized-methodology-to-support-particle-investigations-and-classification-in-biopharmaceutical-parenteral-products/).

Thus, a facility-specific library of the different materials present in the facility (equipment, single-use component materials, consumables, etc), including high quality spectral data (e.g. FTIR, Raman, EDS) becomes a critical support tool for particle risk assessments.

Future-Proof Your Visual Inspection Operations

Define the unexpected

Scientific literature and current regulatory guidance acknowledge the practical reality that achieving completely particle-free sterile manufacturing of parenterals is currently impossible. This doesn't signify a failure; rather, it reflects the nature of the manufacturing process, the materials used and procedures employed. Fortunately, the presence of a very low baseline level of typical process-related particles is not generally considered detrimental to the quality of parenteral drug products (J Ayres 2018: https://pubmed.ncbi.nlm.nih.gov/30158238/). Though the key in guaranteeing a high standard of quality lies in adopting a risk-based approach.

A risk-based approach for particle management in sterile manufacturing is based on differentiating the expected (normal operations) from the unexpected (operational irregularities). By establishing a baseline for what constitutes a "normal particle background" or "**typical process-related particles**", manufacturers can effectively define the "**atypical**". The "typical process-related" particles often originate from equipment and primary packaging wear (e.g. metal, plastic or glass particles) or from consumables, cleaning and gowning materials (e.g. polymer particles and fibers) and despite best efforts and strict particle environment control in the sterile manufacturing facility, cannot be completely eliminated. Understanding and documenting these expected (meaning: unwanted but unavoidable) particles, both in terms of types and frequency of occurrence, is very important for defining the normal operational range of the facility and by inference - what is abnormal/ atypical. A sudden appearance of atypical particles or an increase in occurrence of typical process-related particles, representing a departure from the established norm, may signal a breach of Good Manufacturing Practices (GMP) or a process failure and should

trigger an immediate action (e.g. an investigation). By focusing resources on identifying and addressing deviations that could potentially compromise product quality or safety, this risk-based approach ensures high product quality and consistent production process, while maintaining high operational efficiency (effective use of resources and time).

Establishing a facility particle/ material library is a vital tool in this approach. By collecting and documenting typical process-related particles associated with your specific processes and materials, a facility defines a comprehensive reference point for identifying manufacturing issues. Such libraries can serve as a cornerstone for effective particle control, allowing operations and quality staff to focus on what truly matters – ensuring product quality and safety. The contents of a facility particle & material library can vary and can be adapted as needed, but typically it should include corresponding entries for each material source (e.g. material/ equipment part article number and source), material composition, digital photographs, and critically - spectroscopic analyses data. The latter can be the spectra acquired using FTIR and/ or Raman micro-spectroscopy, Laser Induced Breakdown Spectroscopy (LIBS), energy dispersive spectroscopy (EDS), or any additional analytical data that may help identify particles by matching them to the internal library spectra. It is important to note, that whereas there are a number of publicly and commercially available material spectral libraries, it is of paramount importance to build a spectral library from the exact components and materials used in the given facility. A facility-specific spectral library enables exact match to specific components and materials used in the facility (similarly to a fingerprint database), enabling rapid issue resolution and efficient deviation handling.

In summary, a risk-based approach acknowledges the realities of the manufacturing environment. By setting realistic expectations and focusing on identifying atypical particles, manufacturers can optimize their resources and ensure consistent production of high-quality products. Facility material/ particle libraries are a critical component of a solid control strategy, enabling a scientifically sound, risk-based approach.

Building your defenses - a guide to constructing a facility particle library

Facility particle/material libraries are a game-changer for any parenteral fill & finish facility. They ease investigations, strengthen quality management, and streamline visual inspection operations. While constructing one may seem daunting, this short guide outlines simple steps to get you started.

Two Approaches, One Goal: Building a Comprehensive Library

In building facility material/ particle libraries there are two complementary approaches to building a robust library that can be applied either together or independently:

1. Analyze Rejected Units and Identify Particles:

Units rejected during 100% visual inspection of the filled drug product can be a valuable resource. Analyzing the particles found in these units allows a facility to identify and document recurring types. This provides crucial insights into potential contamination sources within the specific manufacturing process. Importantly, these rejected units do not need to be characterized immediately, but can be set aside and analyzed later.

2. Specimen/ Material Swatch Collection Throughout the Facility:

One does not need to wait for problems to arise, but can take proactive steps by collecting specimens from various materials throughout the facility, prioritizing those in direct contact with the product. This could include samples from equipment/ component surfaces, specimens from filters and tubing, or fibers from cleanroom garments and wipes. By meticulously documenting these "typical process-related" particles, every facility can establish a baseline for use during investigations.

Leveraging Water Runs and Media Fills

Water runs and media fills, simulated manufacturing processes using purified water or a growth medium instead of the actual drug product, can be valuable additions to the facility

library-building strategy. Analyzing particles found in rejects from these runs can reveal potential contamination sources within a facility's infrastructure and processes.

Building at Your Pace: Balancing Resources and Time

The speed at which a facility builds its own library depends on the available resources. An intensive effort can rapidly populate it, but this might not be feasible for everyone. The good news is, one can build a facility-specific library gradually, over time with minimal resource impact. Start by focusing on analyzing particles from rejected units and prioritizing materials like those in direct product contact. As resources become available, expand the library to encompass a wider range of materials and processes.

Partnering for Success: Selecting a Contract Lab

Many facilities lack a dedicated internal investigational or forensic laboratory. Others lack the throughput required for major efforts like a library buildup or major investigations. In these cases a critical decision rests on selecting the right contract partner. Here are a couple of key selection criteria to ensure a successful partnership:

- **Proven Expertise in Parenteral Development and Manufacturing:** Choose a partner with the expertise and understanding of the unique challenges and regulations associated with development and manufacturing of parenteral drug products.
- **Experience with Building and Managing Facility Libraries:** Partner with a lab proven in creating and maintaining robust facility particle libraries. They should have expertise in best practices for sample collection, analyses, and documentation.

Building a facility particle library is an investment in your facility's future. By following these steps and selecting the right partners, you can transform this library into a powerful tool for streamlining visual inspections, optimizing investigations, and ultimately, ensuring the highest standards of quality control for your parenteral products. Remember, a well-constructed library

empowers proactive identification and addressing of issues, fostering a robust and efficient manufacturing process that prioritizes patient safety.

Reducing operational complexity in visual inspection of parenterals

Visual inspection is a critical step in ensuring product quality within manufacturing. However, as limited particle ingress during normal sterile fill & finish operations cannot be avoided, particle investigations and risk assessments are part of the routine operation of every manufacturing facility. Fortunately, facility particle/material libraries can be a powerful tool in reducing operational complexity and boosting efficiency in visual inspection operations.

Faster Investigations and Efficient Deviation Management - A Clearer Picture

Efficient fill & finish operations require nimble investigational support and rapid issue resolution. One of the major advantages of facility particle/ material libraries lies in their impact on the speed of investigations and efficiency of deviation management. Facility libraries serve as comprehensive databases, containing information about the normal baseline particle background, associated with the facility's specific processes and materials. This knowledge base enables rapid classification of every new particle of interest (e.g. a reject unit during 100% visual inspection or AQL testing) as either "typical process-related" or potentially "atypical", greatly streamlining investigations.

Imagine a scenario where a new, unfamiliar particle is detected. Without a facility library, further investigation may become a protracted exercise, costly in time and resources. However, the availability of a good facility library enables a quick comparison of the observed particle to the documented "normal" background of the materials and particles commonly detected in the facility. This allows for a significantly faster and more focused investigation, eliminating wasted effort. By providing a clear understanding of what constitutes a "normal" particle background, staff handling the investigations can dedicate their time and attention to what truly matters – identifying

potentially critical events. This eliminates the need for lengthy investigations into expected particle levels, streamlining quality management. Additionally, risk assessments become simpler in most cases. With a clear understanding of the "normal" environment, assessing potential risks associated with observed particles becomes a more straightforward task.

Efficiency and Quality - A Winning Combination

The benefits of streamlined particle investigations extend far beyond saved time. By focusing resources on identifying and addressing deviations, facilities utilizing material/particle libraries achieve increased operational efficiency. This efficiency translates to cost savings, allowing for better resource allocation across other areas of the manufacturing process.

More importantly, the ability to quickly identify and address potential issues contributes significantly to improved quality management. By proactively addressing quality issues, manufacturers can prevent defective products from reaching the market, ultimately safeguarding product quality and patient safety.

In conclusion, facility particle/material libraries are a powerful tool for streamlining visual inspection operations. By simplifying complexity and boosting efficiency, these libraries empower manufacturers to achieve faster inspections, sharper focus on critical events, and ultimately, a higher standard of quality control.

Continuous Improvement with Facility Particle Libraries

Efficient and robust visual inspection operation is critical in ensuring product quality within sterile manufacturing of parenterals. A great tool for achieving the highest level of quality standards and operational excellence are continuous improvement programs. These programs constitute deliberate, organized and sustained efforts to improve the quality and efficiency of visual inspection and particle management which can encompass various operational aspects. Facility

material/ particle libraries are an indispensable component of any sterile fill & finish facility continuous improvement effort, enabling manufacturers to refine visual inspection operations and achieve operational excellence.

Any continuous improvement program typically involves several steps, eg:

A. definition of the present state,
B. planning and implementation of improvements,
C. review the results,

which are repeatedly cycled through at a defined frequency. Facility particle libraries are essential for supporting all steps of this cycle, because they allow to efficiently establish the current state (the materials and components that serve as a source for particulates in drug products), but also to plan the actions for improvements. These actions may vary: evaluation of an alternative source for a single use component, or a request for improvements to a vendor, for example. However, the improvement actions are always based on identifying the particle sources, which is where facility libraries come in.

Continuous improvement programs for particle load reduction can be especially impactful for facilities manufacturing Cell & Gene Therapy (CGT) pharmaceutical products, which often utilize a large number of single use components that are often manufactured at a small scale and commonly feature particle load higher than the components used in the manufacturing of more conventional pharmaceuticals. High quality spectral libraries of the multitude of materials used in manufacturing CGT products are especially helpful, because they allow for a very accurate spectral match to the exact polymer used in the specific component part, which is unachievable with public and commercial spectral libraries, due to the large variety of polymeric compounds currently in use.

In conclusion, facility particle libraries are an investment in quality and efficiency for sterile manufacturing. By establishing a clear understanding of particle sources, manufacturers can implement targeted improvements throughout the continuous improvement cycle. This not only refines visual inspection processes but also paves the way for operational excellence. For CGT manufacturing especially, with its unique component challenges, high-quality particle libraries are an indispensable tool for achieving the highest standards.

Summary: Visible Particles in Injectables - the Awesome Power of Facility Material Libraries

Facility material libraries play a critical role in sterile manufacturing of injectable drugs. The presence of visible particles in these drugs, while undesirable, is unavoidable. Regulatory guidelines define particles based on their detectability during standardized visual inspections. Assessing particle risk involves consideration of factors like particle origin, nature, clinical administration, and other factors. Facility particle libraries containing material data and spectral analyses become crucial for effective risk assessment.

Building a facility particle library is the foundation for both effective particle control and a risk-based approach to quality management. These libraries help define what constitutes a "normal" level of particles within a facility and enable identification of any departure from that norm. The library content can include information about the material source, photographs, and spectral data for accurate identification. Facilities can build their libraries gradually by analyzing rejected drug units and collecting material samples from equipment and components throughout the manufacturing process. For facilities lacking in-house resources, partnering with a contract laboratory can be a valuable and resource-efficient option.

There are many benefits of implementing a facility particle library. Investigations become faster and streamlined, allowing for quicker identification and focus on critical events. Deviation

management becomes more efficient. Overall quality management and patient safety are significantly improved. Additionally, operational efficiency increases, leading to cost savings. Facility particle libraries also play a vital role in supporting continuous improvement programs within sterile manufacturing.

These libraries are particularly impactful for facilities manufacturing Cell & Gene Therapy products. Due to the high use of various single-use components in CGT manufacturing, high-quality, specific particle libraries are crucial for accurate particle identification, something that cannot be reliably achieved with publicly available spectral libraries.

In conclusion, facility particle libraries are a valuable investment for sterile drug manufacturers, promoting high-quality products and operational excellence.