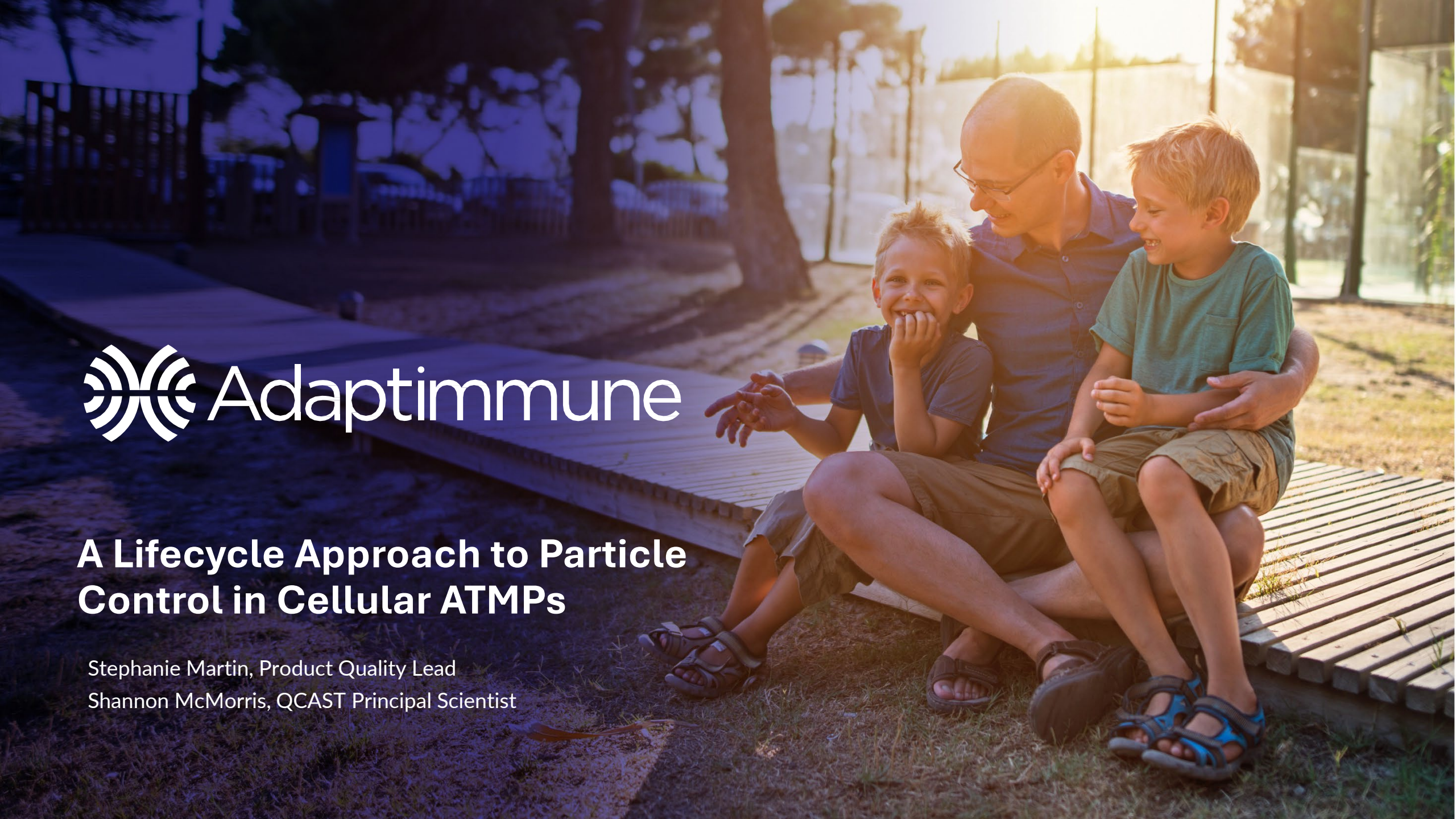

Adaptimmune

A Lifecycle Approach to Particle Control in Cellular ATMPs

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Disclaimer

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Overview

- What are the regulations for particulate matter
- Why is compliance a challenge for Advanced Therapy Medicinal Products (ATMPs)
- How to demonstrate compliance as sponsors and manufacturers
- Implementing a Manual Visual Inspection Program

Five little words…with a big meaning for ATMPs

Essentially free of visible particles

Essentially free of visible particles
Essentially free of visible particles
Essentially free of visible particles
Essentially free of visible particles

Regulatory Expectations

Reference	Requirements & Guidelines
ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products	**The following tests and acceptance criteria are considered applicable to all drug products**… Typical tests found in the pharmacopoeia include, but are not limited to sterility, endotoxin, microbial limits, volume in container, **particulate matter**, uniformity of dosage units, and moisture content for lyophilised drug products.
EudraLex Volume 4, Annex 1: Manufacture of Sterile Medicinal Products	All filled containers of parenteral products should be **inspected individually for extraneous contamination or other defects**.
USP ⟨1⟩ Injections and Implanted Drug Products (Parenterals) - Product Quality Tests	Each final container of all parenteral preparations should be inspected to the extent possible for the presence of observable foreign and particulate matter (hereafter termed visible particulates) in its contents. The inspection process should be designed and qualified to ensure that **every lot of all parenteral preparations is essentially free from visible particulates**.
FDA Guidance for the Industry: Inspection of Injectable Products for Visible Particulates	Noncompendial products should be "**essentially free from visible particles**" as defined in USP General Chapter ⟨790⟩

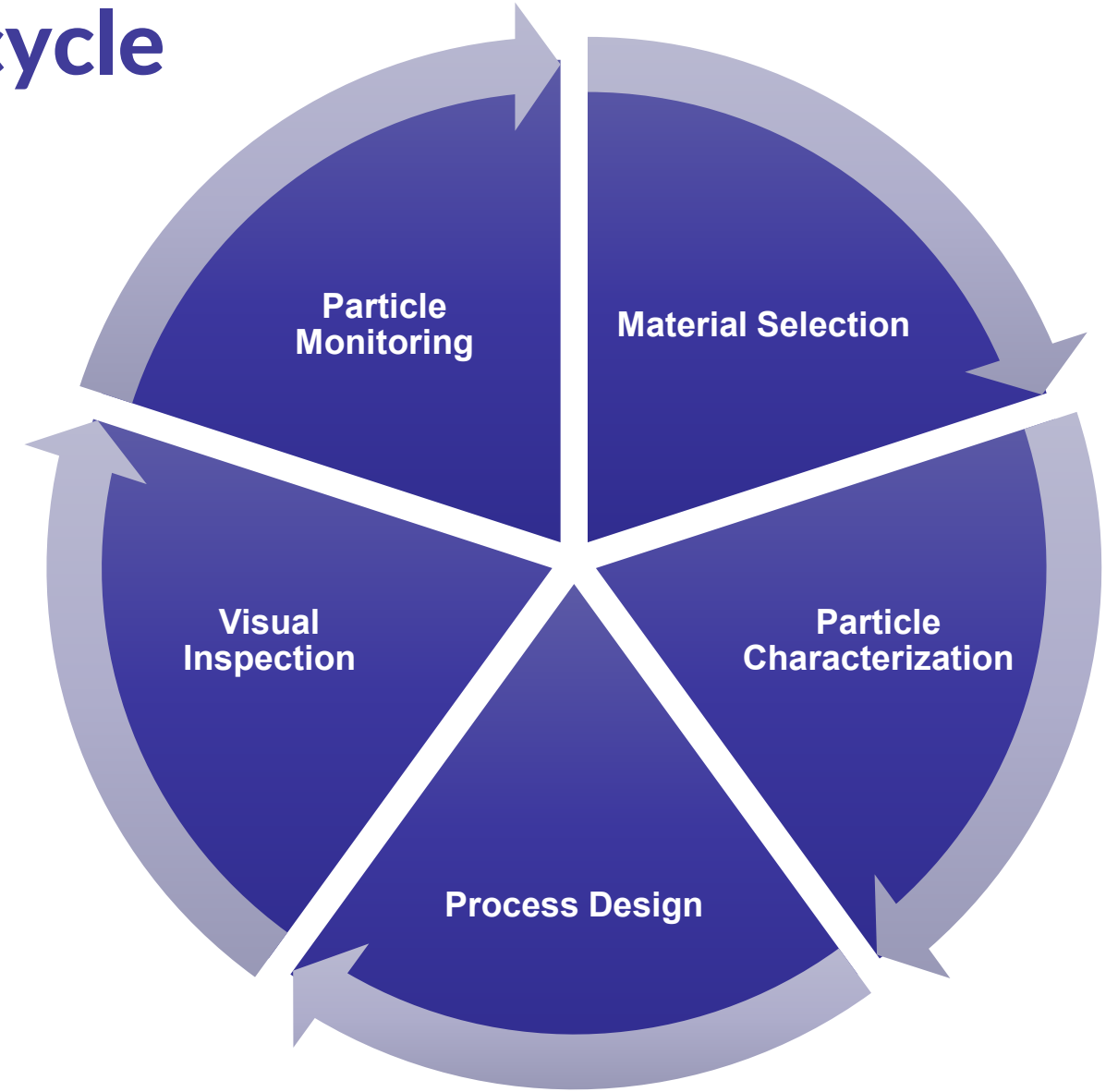
The “Human Expectation”

Deliver safe and effective drugs to patients in need

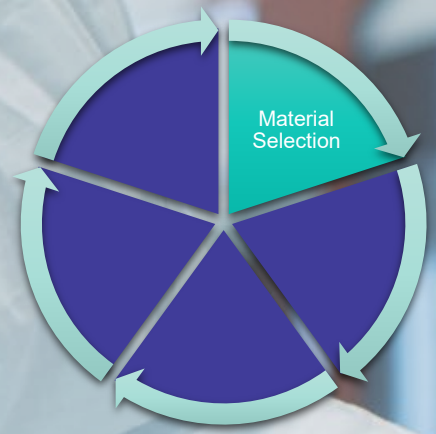
Compliance Challenges

- Larger fill volume
- Cellular material
- Small batch size
- Single-use Systems (SUS) will never be “particle free”

Particle Control Lifecycle

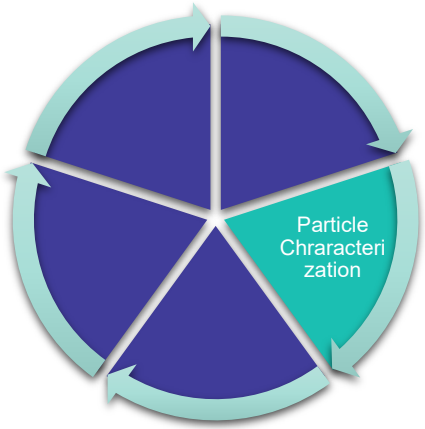


Material Selection



Understand materials of construction	Review the SDS, is the material inert, non-toxic, USP Class VI, or commonly used in medical applications
Particulate Controls	Select materials that require visual inspection as a release criteria or have particulate level claims
Send materials for particle analysis	Conduct rinse studies to understand the particle load of product-contacting consumables

Particle Characterization



Understand Particulate Sources

- Inherent
- Intrinsic
- Extrinsic

Build a Particle Library

- Pictures
- Classification
- Identification

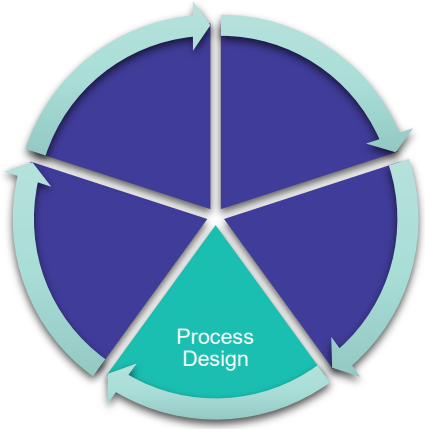
Safety Assessment

- Type
- Size
- Quantity

Particle Characterization – Safety Assessment

Patient Risk Factors
Size
Quantity
Type
Route of Administration
Exposure Duration
Sterility
Aseptic vs. Terminally Sterilized Final Product
Patient Population & Condition

Process Design

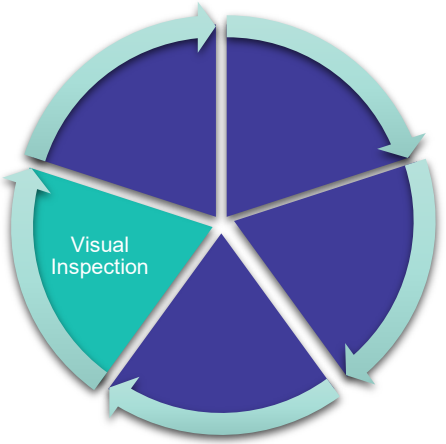


Implement Process Controls

- Inspect consumables for contaminants prior to use
- Rinse or flush components prior to product contact
- Introduce in-line filters

Adding a final filtration step does not alleviate the expectation to control the introduction of particles into the process

Detection of Visible Particles



Classification	Size	Common Detection Method(s)
Sub-Micron	100 nm – 1 µm	Electron Microscopy, Dynamic Light Scattering, SEC
Sub-Visible	1 – 100 µm	Light Obscuration, Microscopic Examination
Visible	**> 100 µm**	**Visual Inspection**, Microscopic Examination

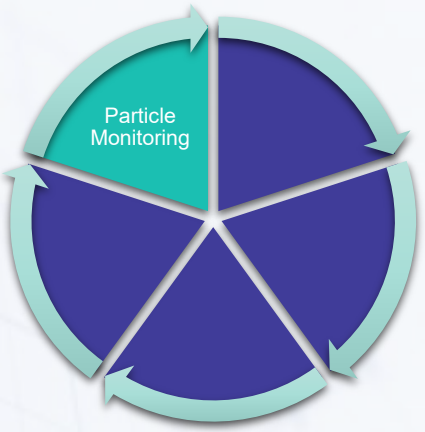
Manual Visual Inspection is the most widely used method to verify product is ***essentially free of visible particles***

Manual Visual Inspection

Compliance with compendial methods USP ⟨790⟩, ⟨1790⟩ and EP 2.9.20

- ✓ Inspection of each container using black and white backgrounds
- ✓ Defined illumination intensity and duration
- ✓ Movement of the container to enhance detection
- ✓ Periodic qualification of inspectors
  - Visual acuity test
  - Use test samples with known defects representative of the Particle Library
  - Account for inspector fatigue
- ✓ Probability of Detection studies

Particle Monitoring



EudraLex Volume 4, Annex 1:

- Defect types and numbers should be trended
- Reject levels for the various defect types should also be trended based on statistical principles
- Impact to product on the market should be assessed as part of the investigation when adverse trends are observed

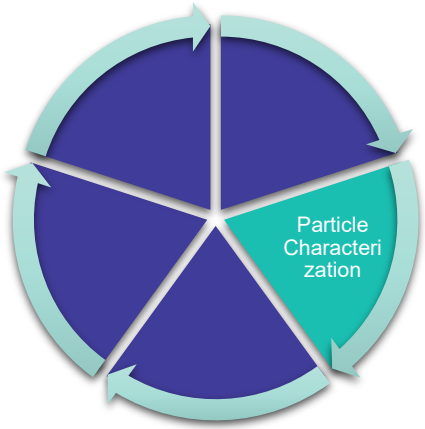
Continuous Improvement

- Atypical inspection results and trends should result in an investigation
- Corrective actions may include changes to materials or additional process controls

Implementing a Visual Inspection Program for Commercial Cell Therapy

- Particle Risk Assessment
- Building a Particle Library
- Establishing Challenge Kits
- Training and Qualification of Inspectors
- Process and Instrument Selection
- Verification of Compendial Method

Particle Risk Assessment



Step 1: Identify higher risk materials used in the process

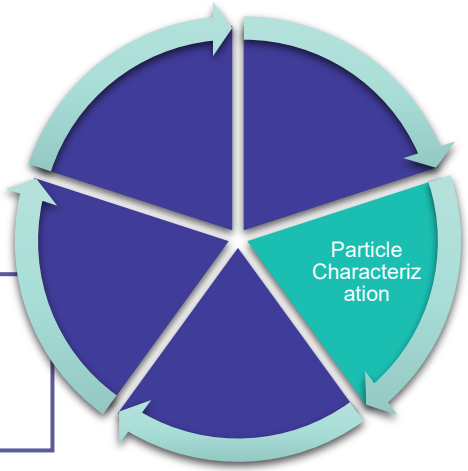
Assess material risk factors				
Surface Area	# of Components/ Complexity	Particle Controls at Manufacturer	Location & Use in Process	Risk Score
5	3	1	3	45

Step 2: Evaluate internal risk reduction measures

Assess material risk factors				
Material Risk Score	Internal Risk Reduction Measures	Effectiveness (% Reduction)	Final Risk Score	Mitigation Plan
45	Visual check prior to use	15%	38	Rinse material prior to product introduction

Step 3: Implement additional controls to achieve acceptable risk

Building Particle Library



Define the **Purpose**

- Training
- Investigation support

Identify the **Scope**

- Product or process specific
- Categorize particulate types

Collection and **Characterization**

- Perform simulated runs and rinse studies of high-risk consumables
- Conduct forensic testing

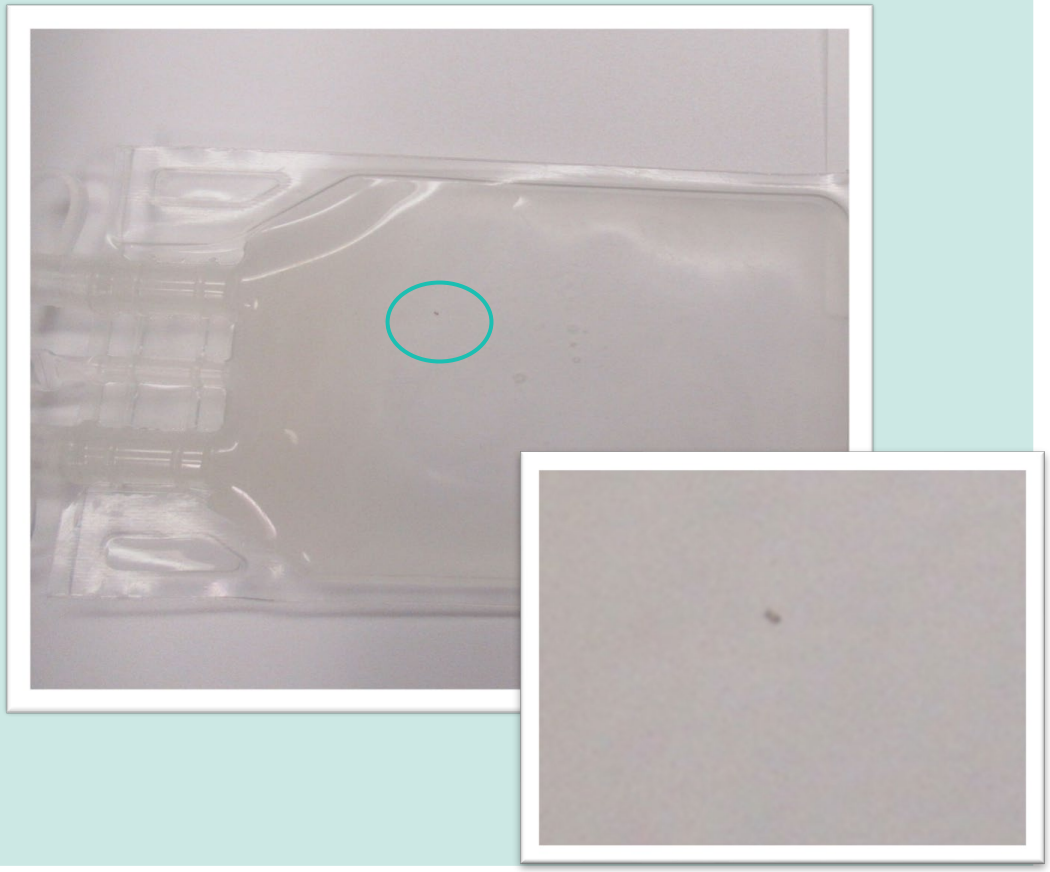
Integrate with **Inspector Qualification**

- Use Library as a training tool to teach inspectors what to expect

Maintain and **Update**

- Periodically review Particulate Library and add new samples

Particle Library Example

Identity	Category	Particle Description	Size (µM) (approximate)	Pictures
Polypropylene	Intrinsic	Dark oval, flake-like	200	

Establishing Challenge Kits

Define Inputs

- Defect types, sizes, quantities
- Sample Size
- Ratio of defect to defect-free bags
- Container and fill volume(s)
- Appearance
- Labeling
- Number of sets

Verification

- Confirmation of defects within bags

Maintenance

- Storage
- Traceability
- Stability over time

Training and Qualification of Inspectors

Initial Screening via Eye Examination

- Visual acuity, 20/20 with corrective lenses
- Color perception

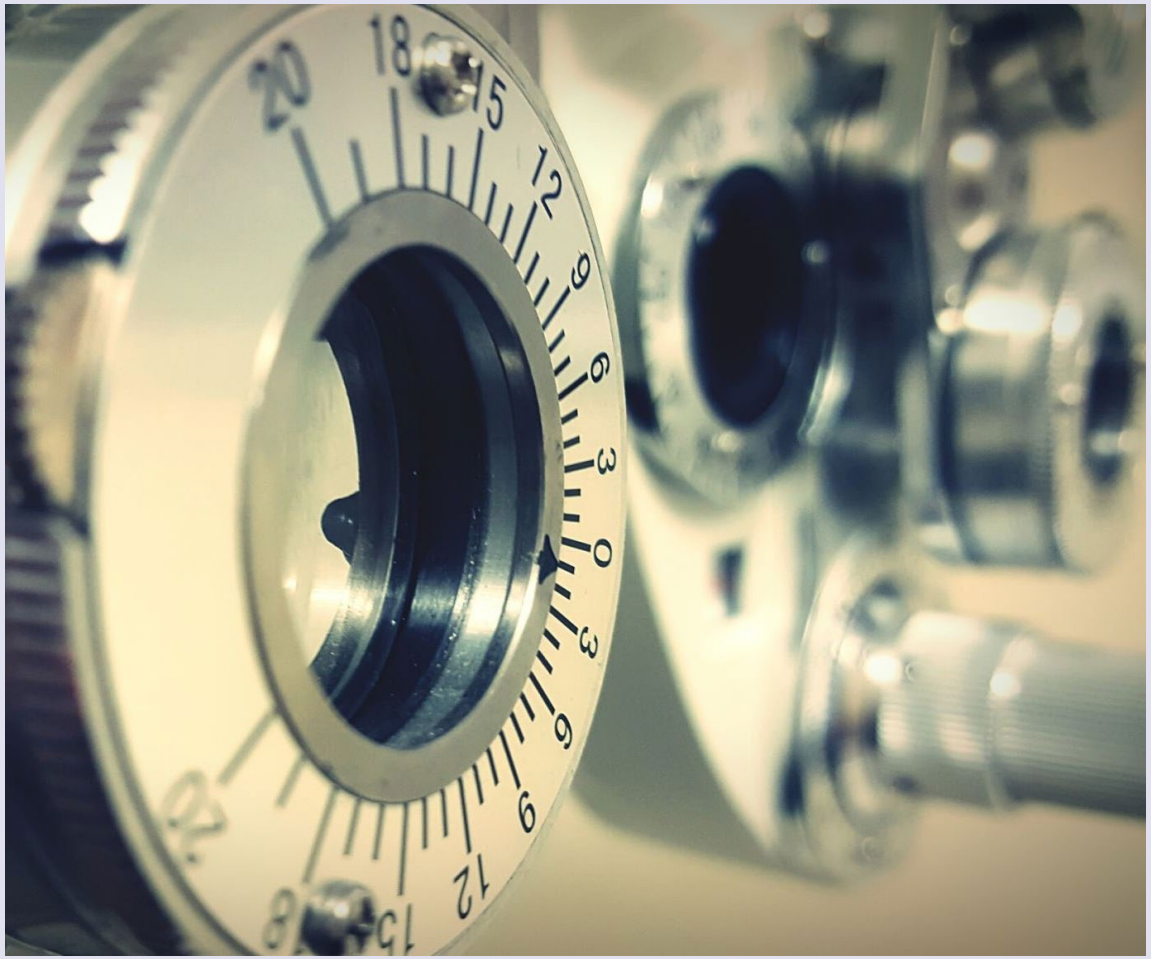
Training

- Classroom
- Hands-on familiarization with samples

Qualification

- Define Probability of Detection
- Inspectors should meet acceptance criteria on 3 independent assays

Periodic re-certification



Implementation at Adaptimmune

Challenge Kit

- 50 Bags per Kit
  - 40 without defects
  - 10 containing defects (100 µm to 600 µm)
- Using final product container and fill volume
- Representative appearance
- Logbook for random numbering system for traceability

Inspector Qualification

- Inspector blindly assessed challenge kits following the method
- Acceptance Criteria:
  - 100% identification of the bags containing particles
  - >90% correct identification of all bags
- Requalification Annually

Process Setup

Standardize and proceduralize best practice amongst inspectors

Movement

Time

Distance

Light intensity

Describe Particles

Shape

Color

Movement

Size

Establish procedure for when particles are observed

Quarantine procedure

Investigation steps

Reference Particle Library

Forensic testing

Toxicology assessment

Instrumentation

USP <790>, Ph. Eur. 2.9.20

- 5 seconds against a black background
- 5 seconds against a white background
- 2000 to 3750 lux

- Qualify Equipment

Additional Equipment

- Calibrated light meter
- Microscope

Verification of Compendial Method

USP <1226> “Verification requirements should be based on an assessment of the complexity of both the procedure and the material to which the procedure is applied”

Demonstrate method suitability

- Accuracy
- Precision

Example Study Design

- 3 operators independently assess the challenge kit
- Results should align between operators and be correct

Harmony between the Lifecyle Approach & Regulatory Expectations

Cited from FDA Warning Letters

"There was no characterization of the particulates found in the batch to determine if they were intrinsic, extrinsic, or inherent to the product" → **Particle Characterization**

"Provide a comprehensive list of all items that could trigger the initiation of an investigation related to foreign particulates" → **Material Selection, Particle Characterization**

"Quality personnel have not maintained a defect library for training purposes or reference" → **Particle Characterization**

Harmony between the Lifecyle Approach & Regulatory Expectations

Cited from FDA Warning Letters

"Visual particulates in injectable products should be avoided through appropriate preventative measures built into your design and production controls" → **Material Selection, Process Design**

"Your firm failed to provide adequate challenge test set vials to qualify your operators to perform the visual inspection" → **Visual Inspection**

Your operators performing manual visual inspections were not adequately qualified for their ability to identify these defects. For example, your qualification kit qualified the operators' ability to identify particles as low as **(…)** micrometers. However, commercial drug product lots investigated for contamination found particulates as small as 150 micrometers.→ **Visual Inspection**

Harmony between the Lifecyle Approach & Regulatory Expectations

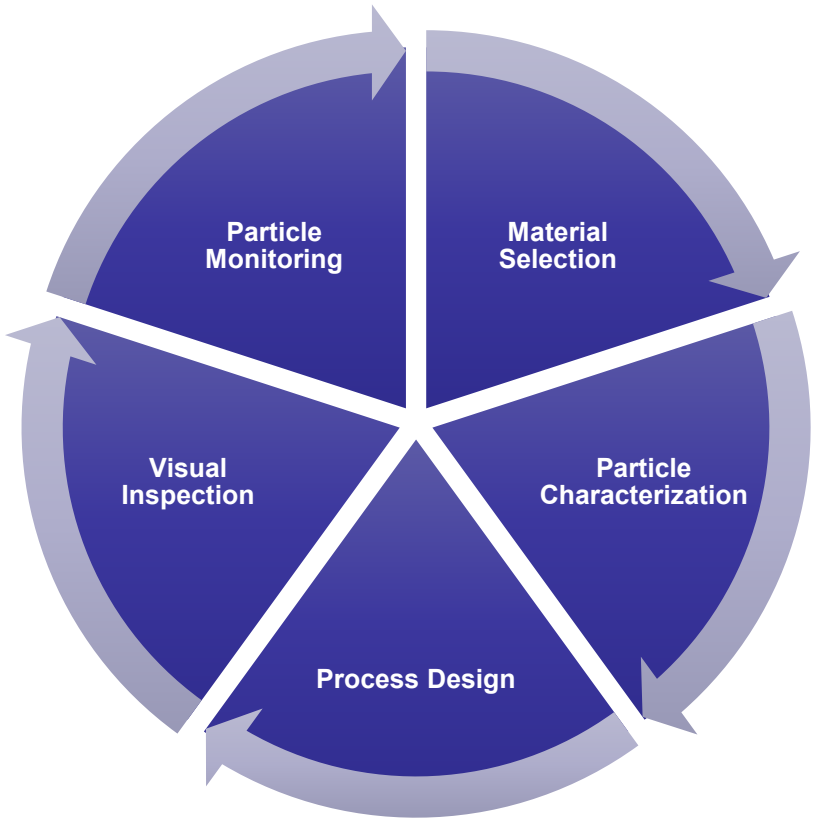
Cited from FDA Warning Letters

"It is important that any visible particulate contamination is appropriately evaluated and investigated" → **Visual Inspection, Particle Monitoring**

"Your firm does not have an adequate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality" → **Particle Monitoring**

Key Learnings

- Regulators require final product to be “essentially free of visible particles”
- This will continue to be a challenge to ATMP manufacturers as single-use systems will never be “particle free”
- Implementing the Particle Control Lifecycle…
  - ✓ Demonstrates material and process controls were selected with particle reduction at the forefront
  - ✓ Understanding the source, types, sizes, and quantities of particles present in the process
  - ✓ Provides confidence in the detection of visible particles through Visual Inspection
  - ✓ Allows for timely identification of issues and continuous improvement




Thank you.
Questions?
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