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Particulate Matter:
USP Requirements and Particle Identification

Bryan Wickson 2019-04-18

Background

- I have worked at Exova for 19 years
- First 8 in the field of polymers and medical device development
- Last 11 year testing of materials and pharmaceuticals
- Mainly spectroscopy and physical characterization

- Exova has 3 GMP labs:
  - Toronto
  - Delaware
  - Santa Fe Springs

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Background

- Formulation development
- Clinical trials manufacturing
- Compendial testing, development and validation
- E&L plus stability studies

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Agenda

- Review of USP Requirements
- Approaches to Identification of Particulate
- Case Studies

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Biological Response

Particles in the vascular system:

- blockages
- emboli
- accumulation/chronic damage to organs

Extravascular particulate:

- immune responses
- eye/tissue damage

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Biological Response

Real Life Examples:

- Glass fragments in inhalers
- Aluminum slivers in ophthalmic eye drops

- Rubber o-ring pieces in IV solutions

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Background

Particulate matter testing of pharmaceutical parenteral solutions is governed by:

- USP<1>Injections and Implanted Drug Products
- USP<1790><790>Visual Inspection of Injections
- USP<1787><787>Sub-visible Particulate Matter in Therapeutic Protein Injections
- USP<1788>Particulate Matter in Injections and Ophthalmic Solutions
- USP<788>Particulate Matter in Injections
- USP<789>Particulate Matter in Ophthalmics

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Background: USP

Particulate matter can be defined by size:

- Visible particles: ≥ 100 µm
- Sub-visible particles: < 100 µm

And by source:

- Inherent
- Intrinsic
- Extrinsic

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USP<1>

"Should be prepared in a manner designed to exclude particulate matter"

"Each final container of all parenteral preparations should be inspected to the extent possible for the presence of visible particles"

"Every container in which the contents show evidence of visible particulates must be rejected"

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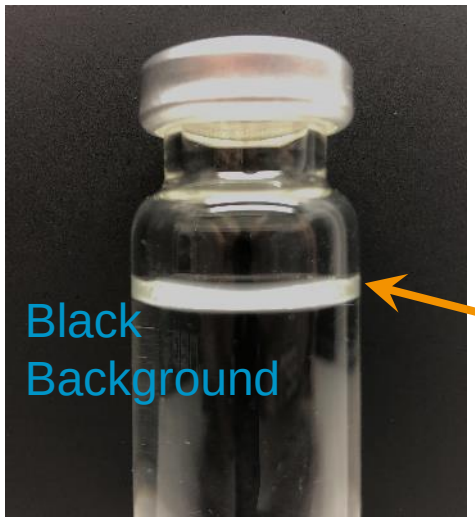
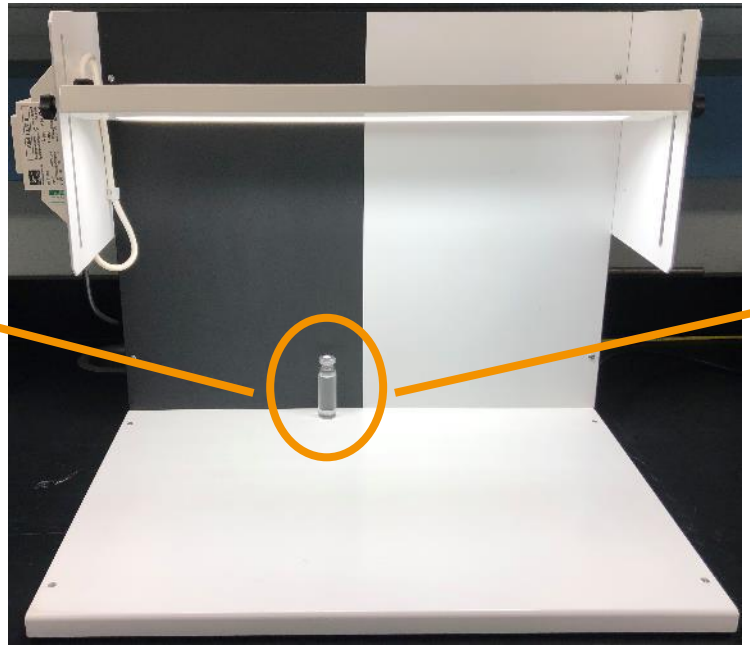
USP<790> Visible Particulate

- Specific lighting with different backgrounds
- Operators are trained and qualified





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USP<787><788><789> Sub-visible Particulate

- No visible particles are allowed
- USP contains limits for sub-visible particles

- Method I: Light Obscuration Particle Count
- Method II: Microscopic Particle Count

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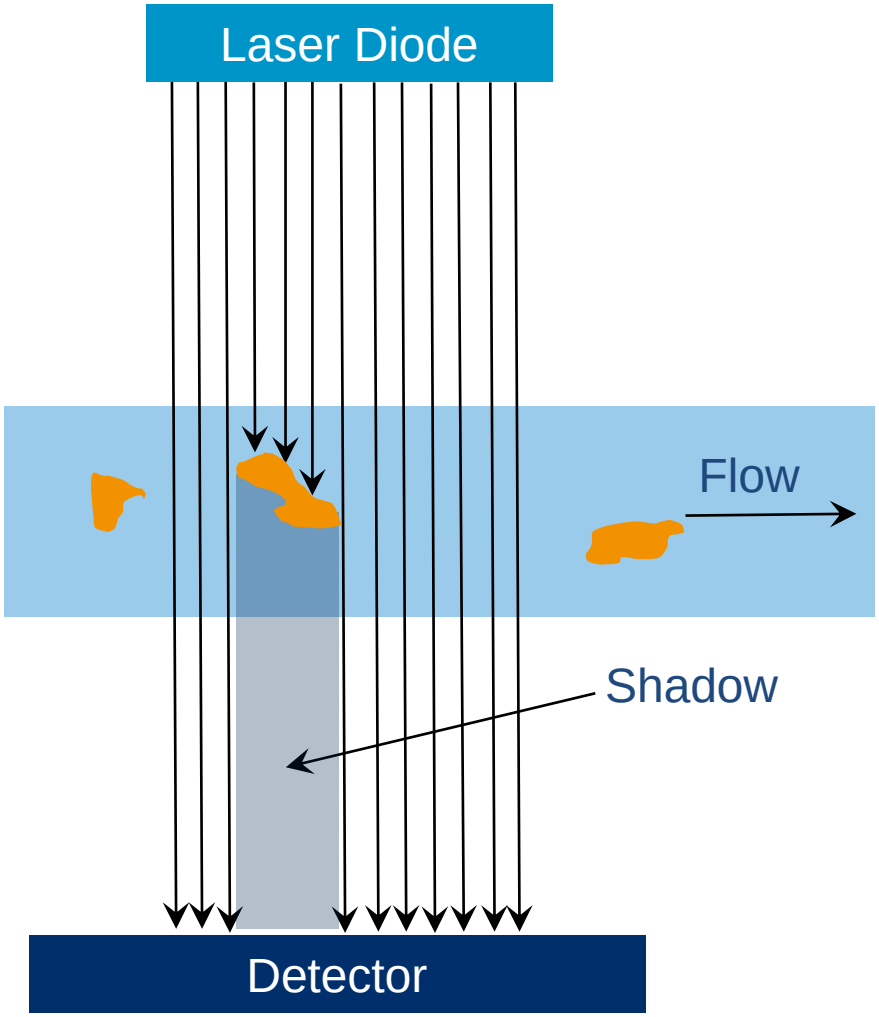
Method 1: Light Obscuration

The technique involves directing a laser through a dilute solution

Instrument counts and sizes particles



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Method 1: Light Obscuration

Pros

- 1-600 microns
- Fast and repeatable
- Recommended by USP

Cons

- Provides “average” particle size
- Instrument accuracy
- Bubbles

NOTE: The method should be verified for the specific product and any unusual sample preparation

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Method 2: Microscopic Particle Count

Sample is filtered

Particles are sized/counted by using light microscopy:

- Manual counting
- Automated stage/Image analysis
  (good for high volume QC testing)

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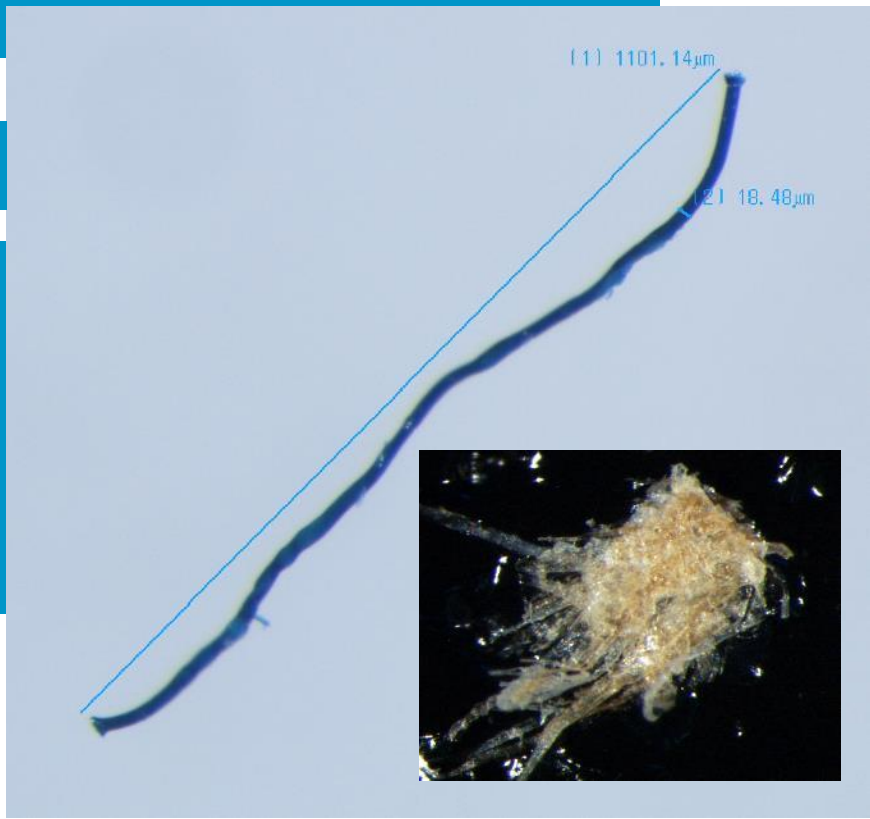
Method 2: Microscopic Particle Count

Pros

- Potentially more accurate that Method 1
- Not impacted by artefacts such as bubbles
- Appearance of particle

Cons

- More time consuming
- Image analysis requires validation/verification
- Open to interpretation…



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Next Steps

An investigation is required to determine the nature and source of the particulate

Investigative analysis:

- Validated methods are not required

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Contaminant Analysis

Identification of particulate

The particulate may be visible or sub-visible

Identification is key:

- Improve processes
- Maintain regulatory compliance

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Contaminant Analysis

How are the particles found?

- Incoming inspection of raw materials
- Operators
- QC inspections of final product
- Pharmacists/nurses
- Patients

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Contaminant Analysis

Impact of contaminant analysis

Potential outcome:

- Normal release of the final product
- Process modification
- Substitution of process equipment
- Rejection of a Lot of raw material
- Rejection of a final product
- Product recall

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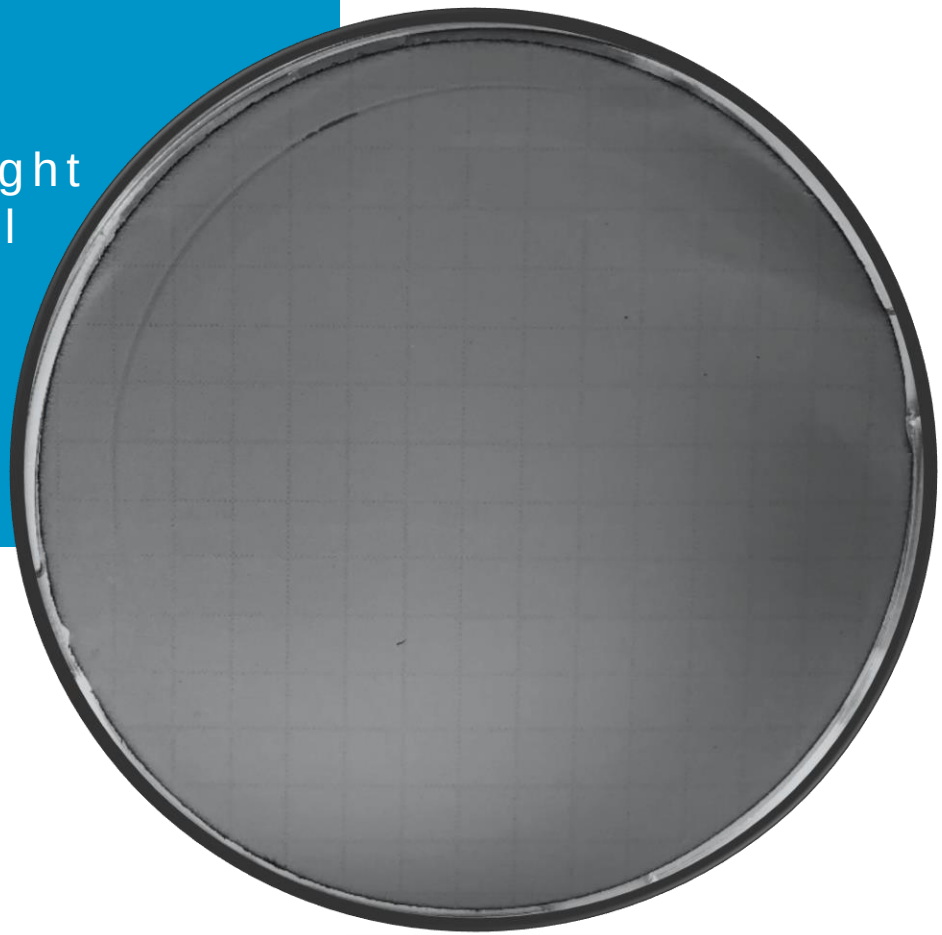
Sample Preparation

- Filtration (USP <788> Method 2)
- Centrifugation
- Manual removal with light microscope and scalpel
- Solvent extractions/rinsing



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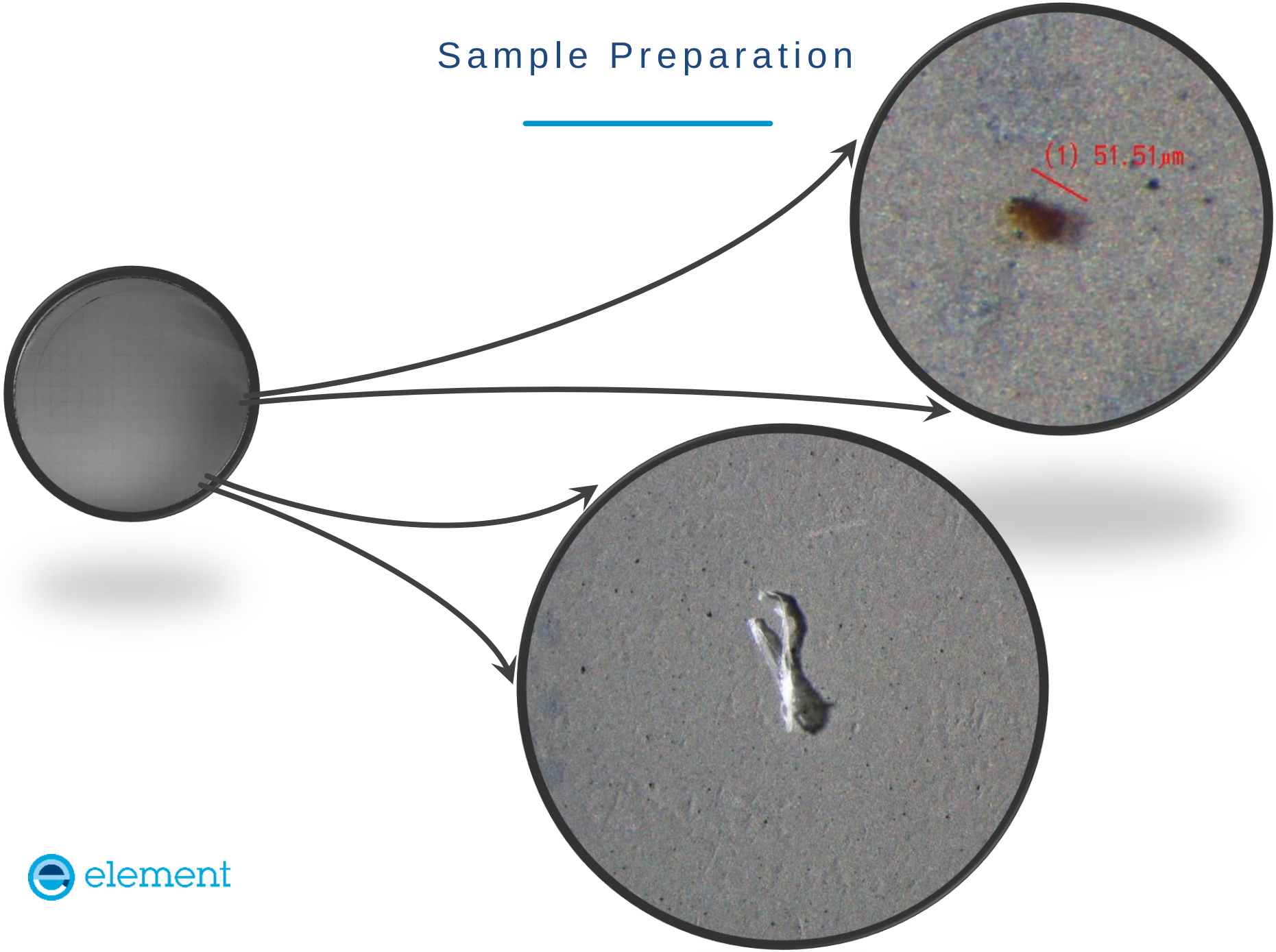
Sample Preparation



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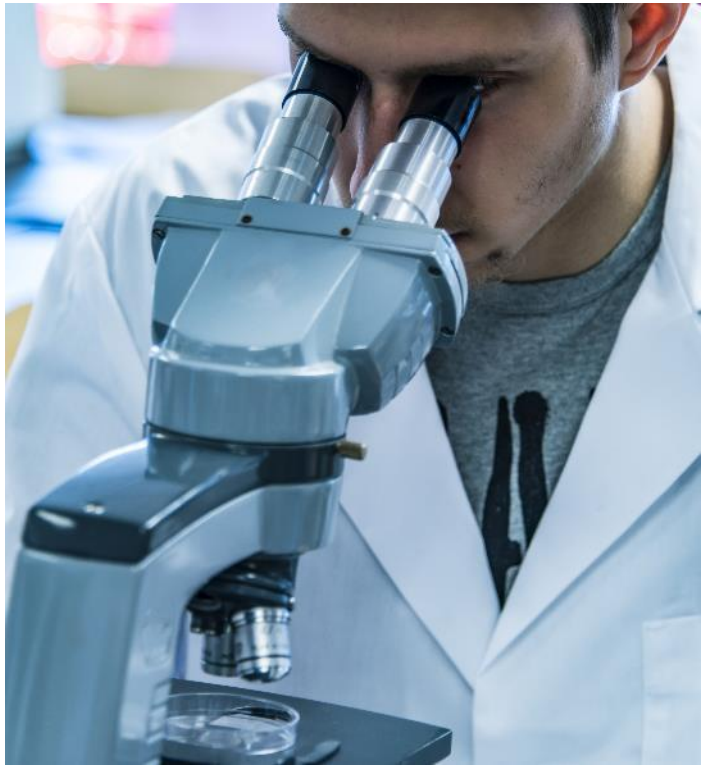
Analytical Tools

Techniques must be suitable for analyzing micron sized particles typically weighing less than a few micrograms

These include:

- Light microscopy
- SEM and SEM/EDS
- Micro-FTIR spectroscopy



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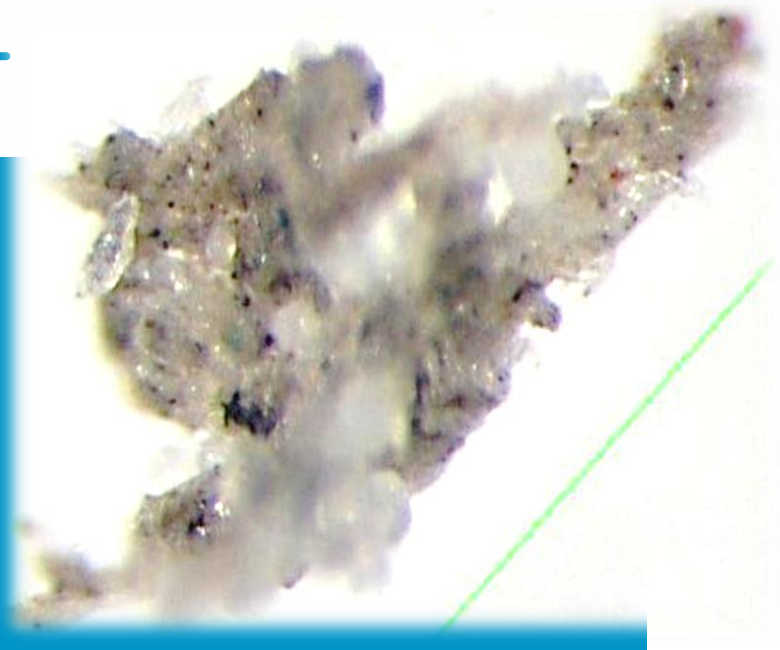
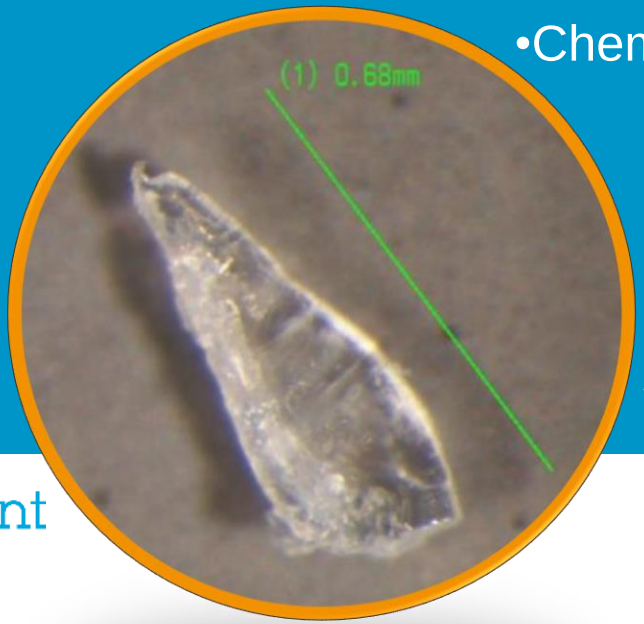
Light Microscopy



- Colour and size of a contaminant
- Physical nature of the contaminant:
  - Gel-like
  - Solid (crystal, amorphous or fiber)
- Heterogeneity of the contaminant



- Chemical nature of the contaminant:
  - Organic material
  - Polymeric material
  - Inorganic (e.g. salt or metal)
- Recommendations for analysis starting point

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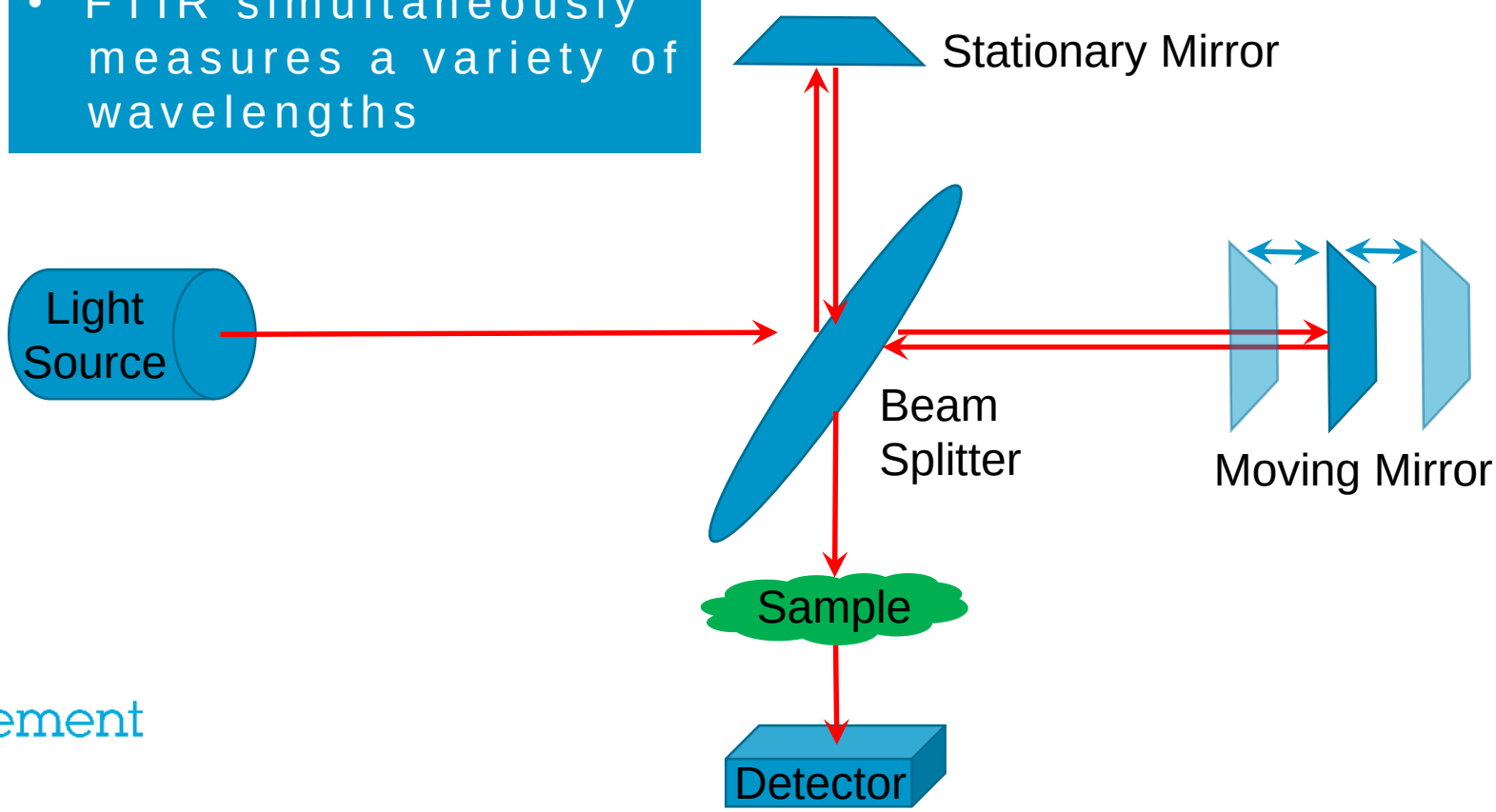
FTIR Spectroscopy

- FTIR is similar to UV-Vis
- Light is passed through a sample and the absorption of light is measured.
- UV-Vis sends 1 wavelength at a time
- FTIR simultaneously measures a variety of wavelengths



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FTIR Spectroscopy

- The radiation causes the sample to vibrate and absorb energy
- Different molecular bonds absorb at different characteristic frequencies
- Different bonds can vibrate in multiple different manners (bending, rocking, stretching) resulting in multiple absorbances
- The IR signal can transit through a sample or graze (reflect) off a sample surface (ATR technique)

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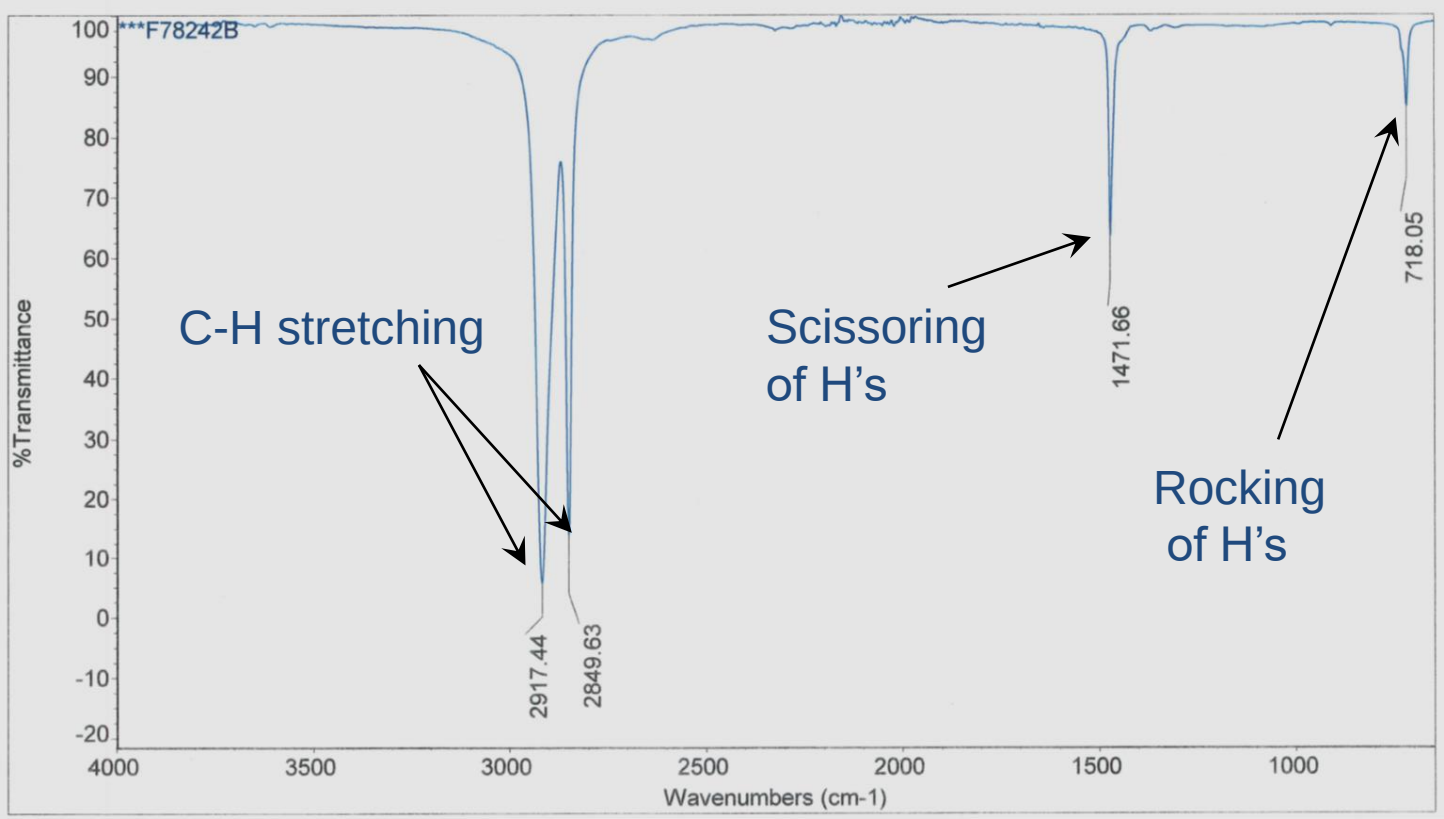
FTIR Spectroscopy

- Here is an example Polyethylene spectrum
  $-(-CH_2-CH_2-CH_2-)_n-$



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FTIR Spectroscopy

Can be used to analyze 10-20 µm sized particles

The spectrum can be compared reference spectra

FTIR is best suited for polymers and organic materials

Mixtures of materials can be identified by using spectral subtractions

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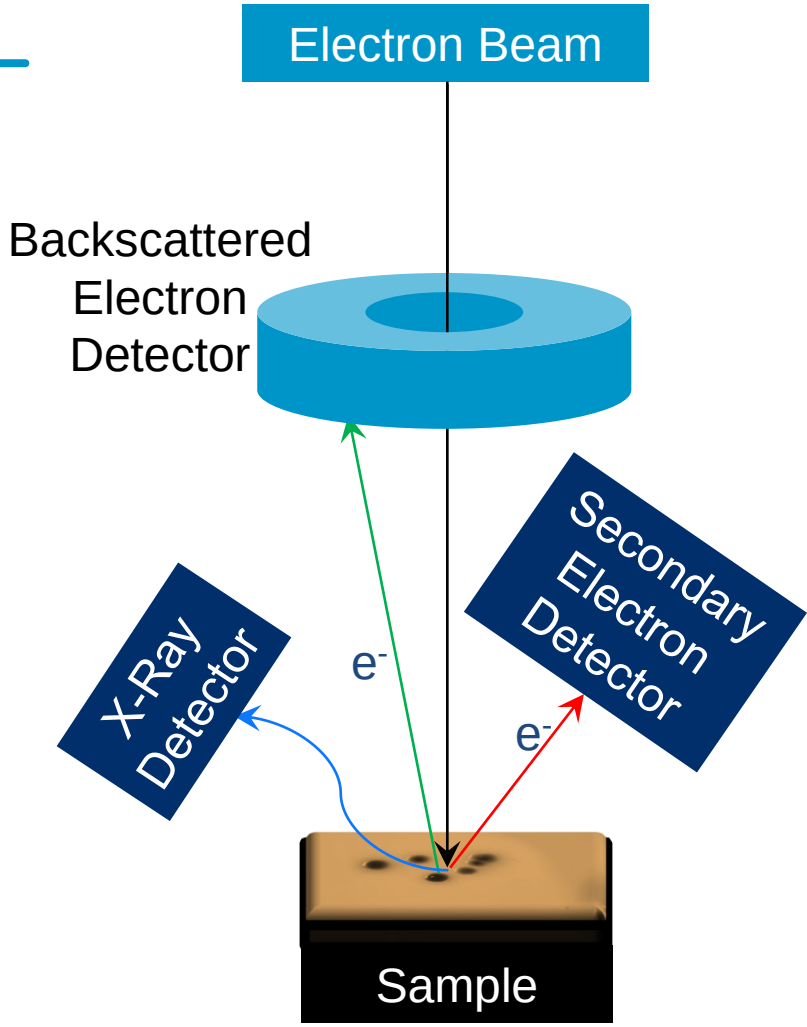
SEM/EDS

- SEMs are traditionally used to obtain morphology of conductive materials (i.e. metals)
- This is performed by collecting emitted secondary electrons emitted from a surface

- Collection of emitted X-rays allows for the determination of the source element



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SEM/EDS

SEM provides high resolution photos of conductive and non-conductive materials

When coupled with EDS, it can also provide elemental composition information

SEM/EDS is semi-quantitative: most quantitative when the sample is an ideal flat surface of heavy elements

When the surface is not flat (typical for contaminants) and comprised of lighter elements (e.g. C, N, O), it becomes less quantitative

SEM/EDS is ideal for heterogeneous materials since the EDS spot size can be as small as 1 µm

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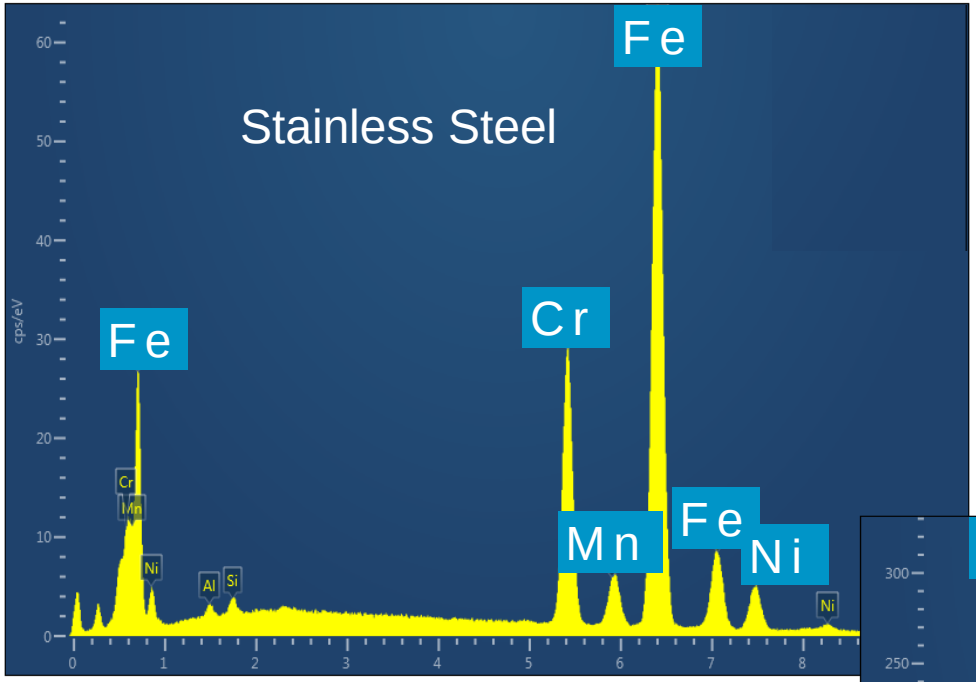
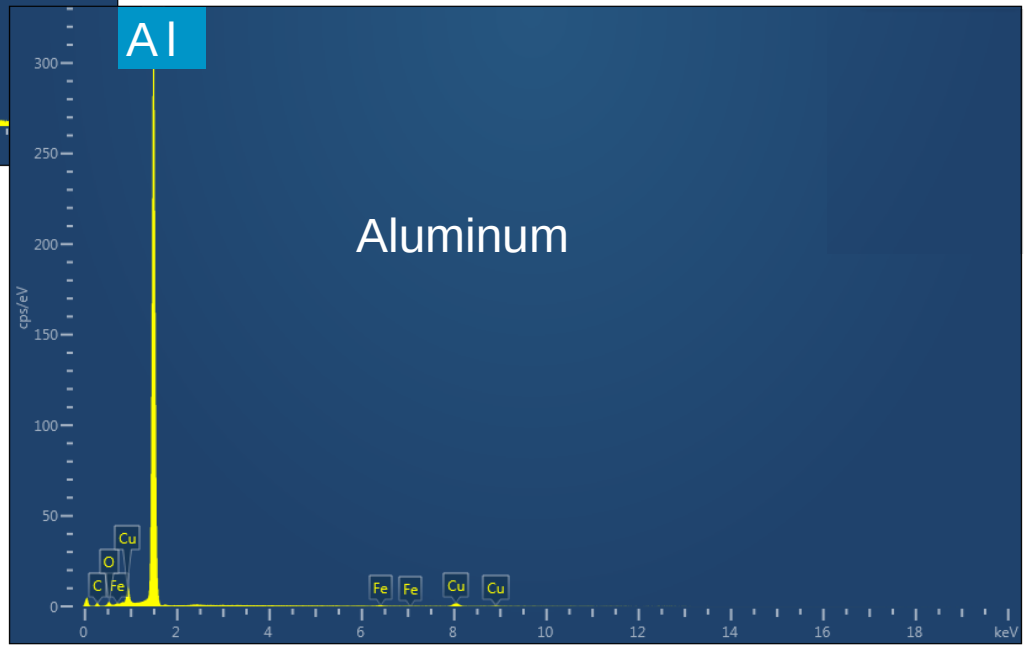
SEM/EDS





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How Can You Help?

Background information:

- Ingredient list and SDS's
- H&S handling instructions
- How and when the product was discovered
- Suspected reference samples, such as:
  - Labels/packaging container
  - Gaskets/tubing
  - pump oil
  - grease
  - mixing blade
- Raw materials as references

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Case Study #1

What is that particle inside of the pre-filled syringe?

- Upon initial examination we could see a greyish particle inside of a pre-filled syringe.
- The plastic syringe was cut open and examined by light microscope. The particle was observed sitting on the barrel surface.
- We proposed to obtain photos of the particle and then analyze it by FTIR and SEM/EDS.

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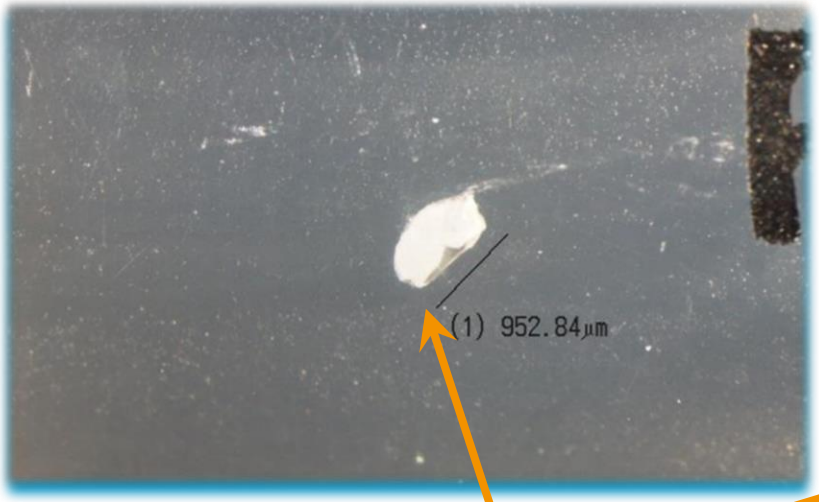
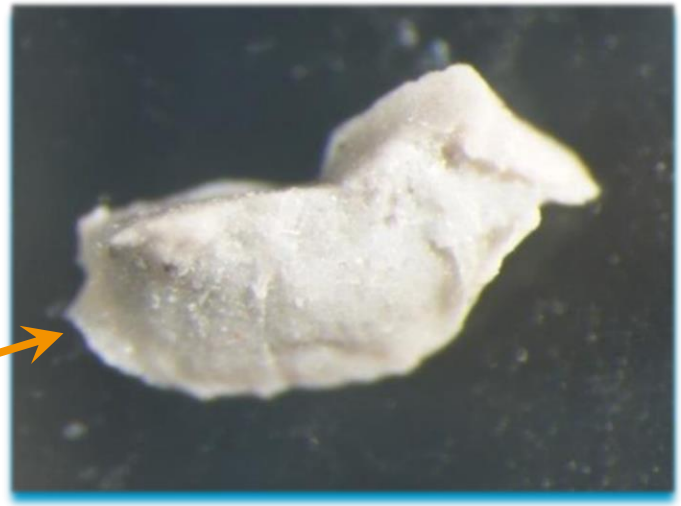
Case Study #1



Light grey particle on syringe wall



Magnified

Light microscopy and manual probing showed the particle to be grey, opaque and elastomeric.

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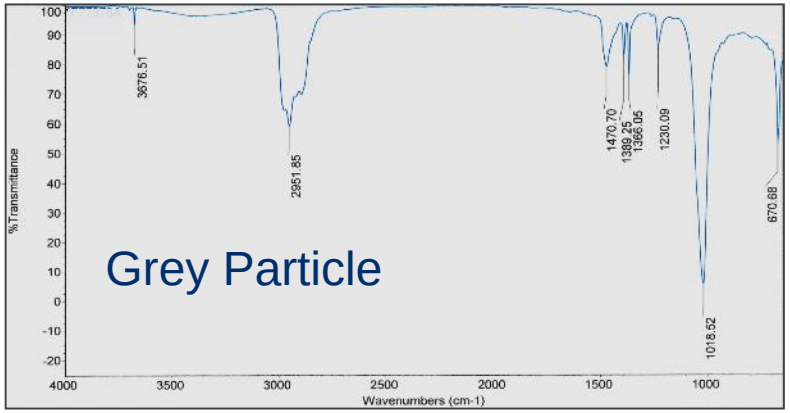
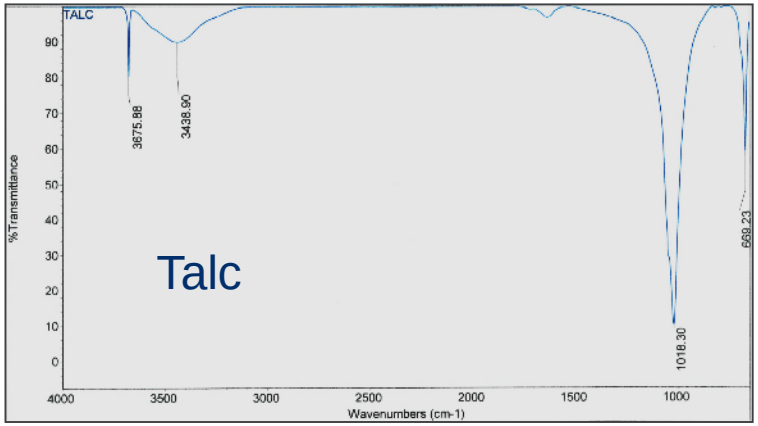
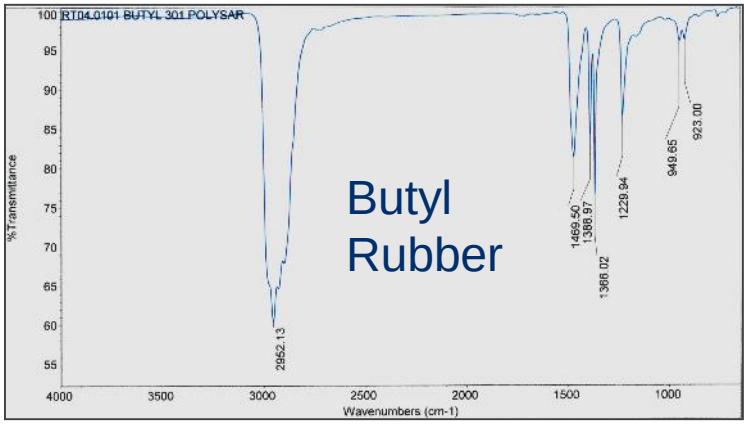
Case Study #1







FTIR showed the particle to match that of a filled butyl rubber

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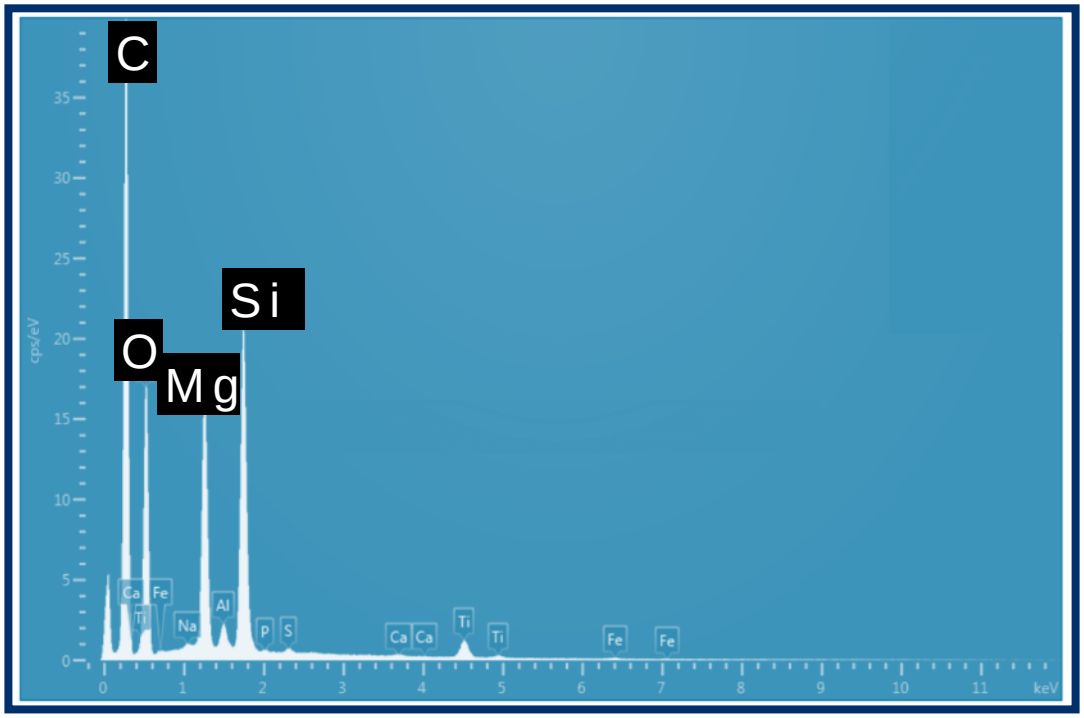
Case Study #1



Analysis by SEM/EDS showed C, O, Mg and Si as predominant elements

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Case Study #1- Conclusions

The light grey particle is a talc filled butyl rubber

Syringe plunger septum!!!

The septum is a black rubber, so it is ruled out as a potential source of the particle

We recommended that the client audit their manufacturing process with respect to light grey rubber sources (e.g. gaskets, o-rings, septa)

They could also approach their suppliers as the particle may have an upstream source

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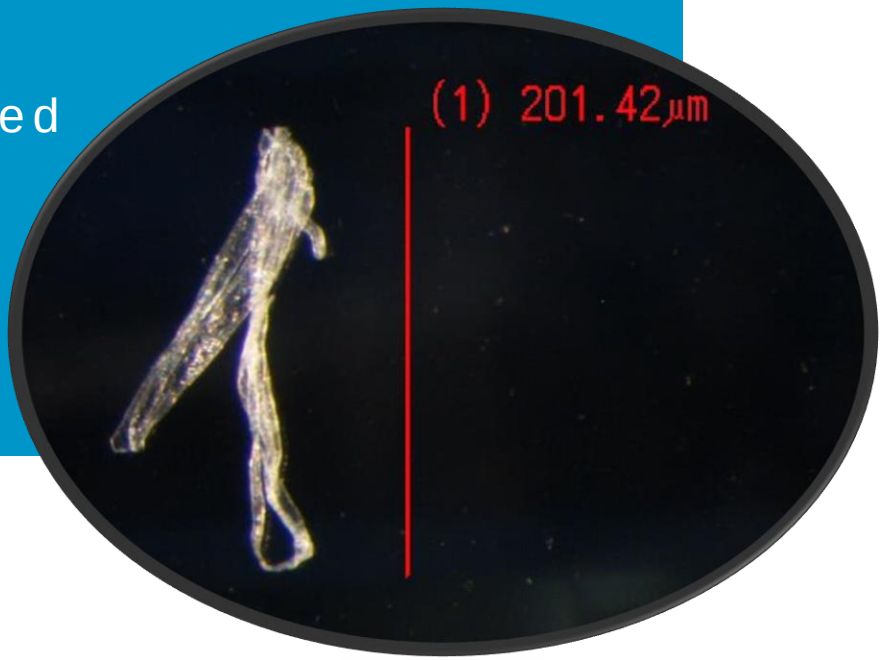
Case Study #2

What is that floating in the vial?

- During routine QC testing by USP <790>, a rejected vial was set aside for subsequent investigation
- Initial examination revealed a fiber
- We proposed to analyze the fiber by micro-FTIR



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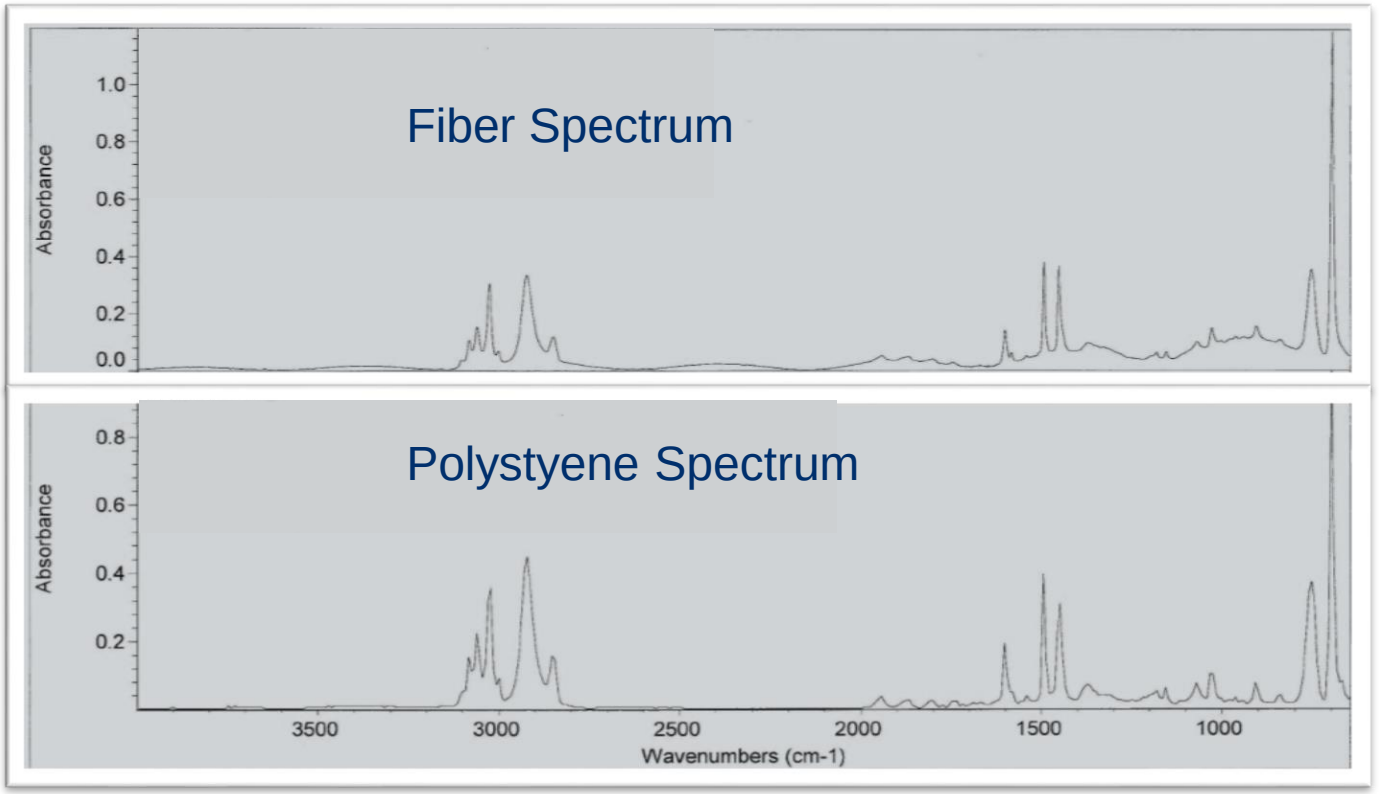
Case Study #2



Light microscopy- fiber with a flat profile
FTIR analysis identified the fiber as polystyrene.

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Case Study #2- Conclusions

The fiber was identified as polystyrene

The plastic vial was analyzed and found to be polystyrene

The vial is the likely source

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Case Study #3

What are those particles I can't even see?

- During QC testing by USP <788> Method 1, passing results were obtained, however the counts were higher than expected.
- The product was filtered. Examination of the filter showed dark particles with sizes in the range of 25 microns.
- We proposed to analyze the particles by FTIR and SEM/EDS.

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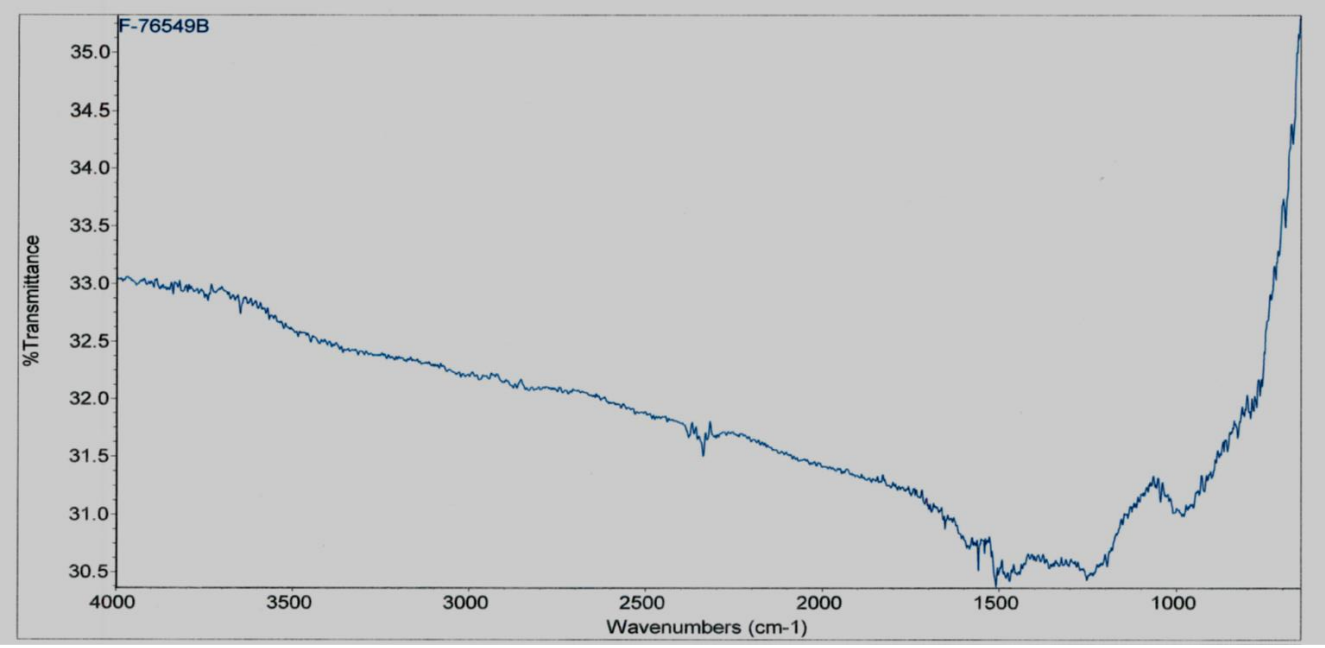
Case Study #3



We were not able to obtain a useful FTIR spectrum

The particle is highly absorbing or reflective

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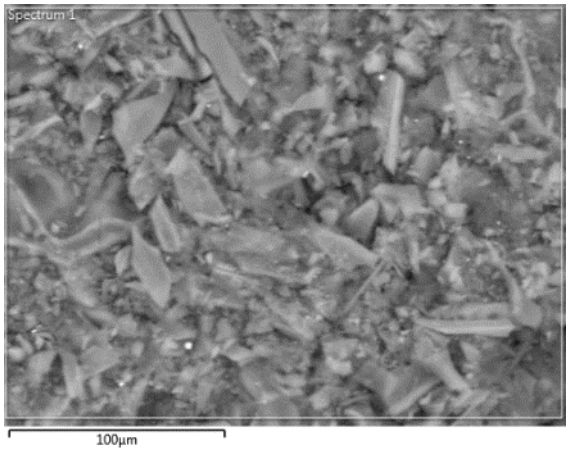
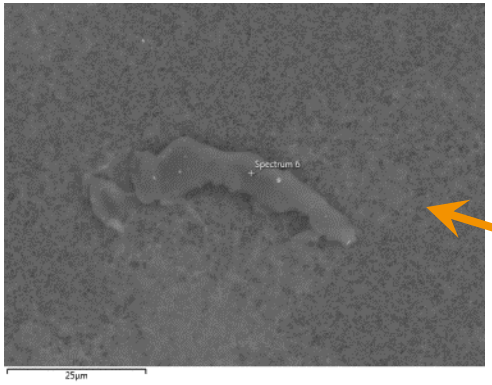
Case Study #3

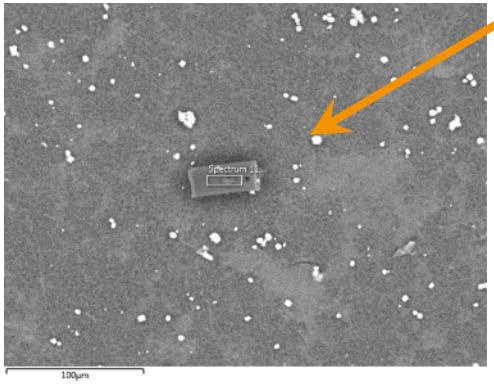
SEM confirmed the particle sizes and shapes.

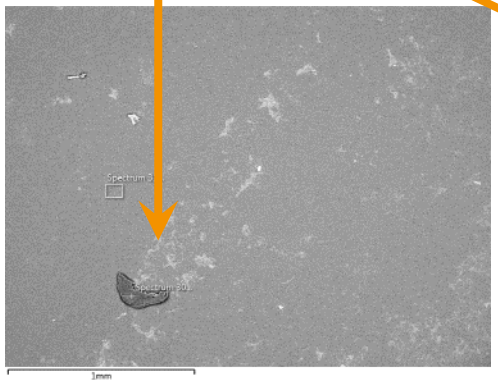


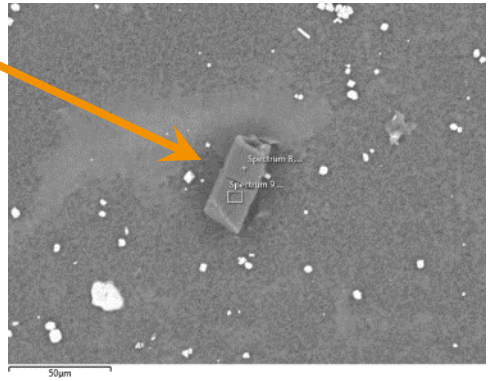
Reference Charcoal



Filtered Particulate







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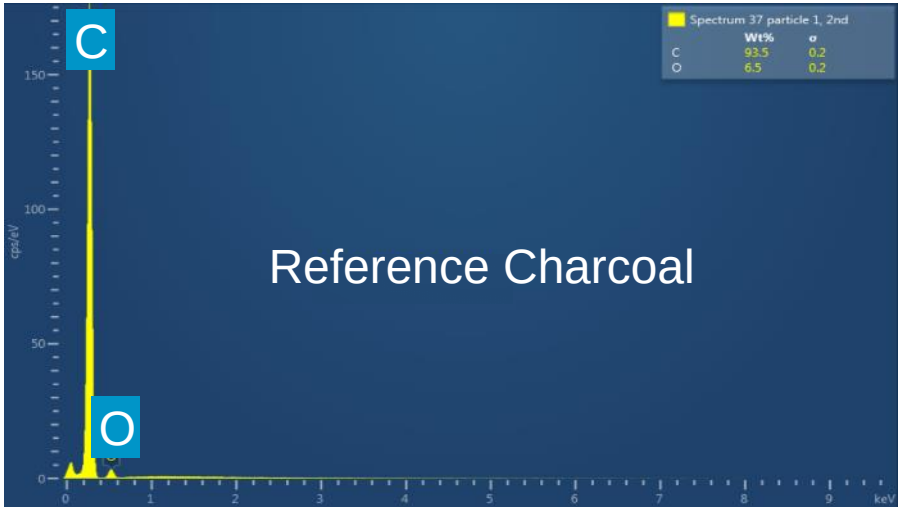
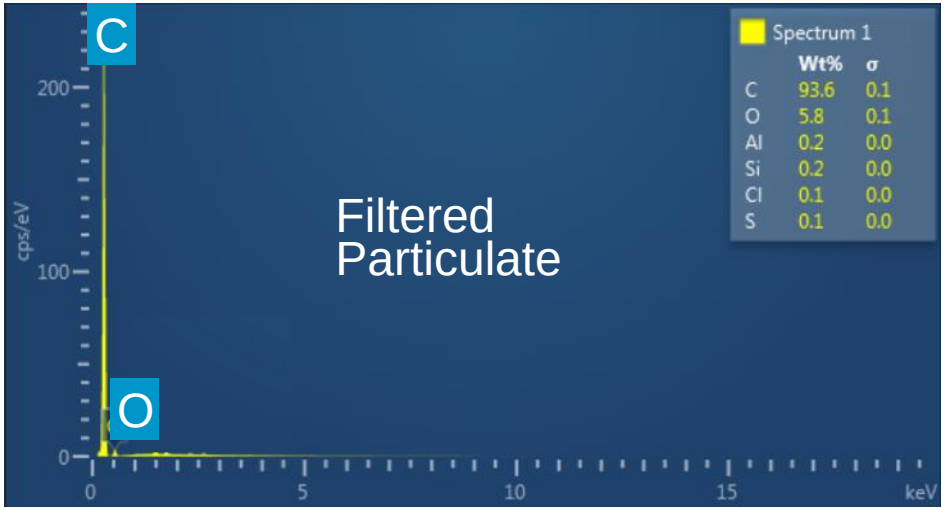
Case Study #3

Elemental comparison





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Case Study #3- Conclusions

Based on FTIR spectroscopy, SEM and EDS analysis the sub-visible particles were identified as charcoal

Activated charcoal is used in their processes as a filtering aid

The manufacturing process did not fully remove the charcoal from their product

Why??

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Case Study #4

My parenteral is not a clear solution.
Now what?

- Suspensions
- Emulsions
- Implantable Drug products

USP< 1>

“Each final container of all parenteral preparations should be inspected to the extent possible for the presence of visible particles”

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Case Study #4

This example will address a parenteral implantable protein matrix/drug product

An FDA review concluded that the current inspection of the article surface is not adequate

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Case Study #4

Approach 1

- The protein based product was digested/dissolved in a caustic solution
- Time, caustic strength and heat were investigated
- The resulting low viscosity solution was filtered through a 10 micron stainless steel screen
- Undissolved particulate was quantified as follows:
    - By weight
    - Visual examination (counts, size and description)
    - Particles were then identified by FTIR and SEM/EDS

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Case Study #4

Approach 2

- The protein membrane was hydrated in saline for 5 minutes to simulate actual OR practice Saline sample 1
- The hydrated membrane was transferred to fresh saline and then gently swirled for 15 minutes Saline sample 2
- Both saline solutions were analyzed by USP <788> Method 1 and 2
- Saline sample 2 represents “loose” particulate that would be implanted

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Case Study #4

Both approaches were seen as screening investigations to provide an understanding as to the number and type of particles involved with their product

The data was submitted to the FDA

A validated QC method for this product has not yet been developed and validated

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Concluding Remarks

Analytical characterization of parenteral products is a common and well understood requirement

The FDA requires definitive physical characterization of particulate matter in parenteral products

The objective to minimize and eliminate particles is based on the ultimate goal of patient safety

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Thanks for coming tonight!

Thanks for lending Jeremiah Masoli to the Tiger-Cats!

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Particulate Matter

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Questions??

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