Current USP Standards for Particulate Matter

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USP/IQ Consortium Hybrid Roundtable on Subvisible Silicone Oil Droplets
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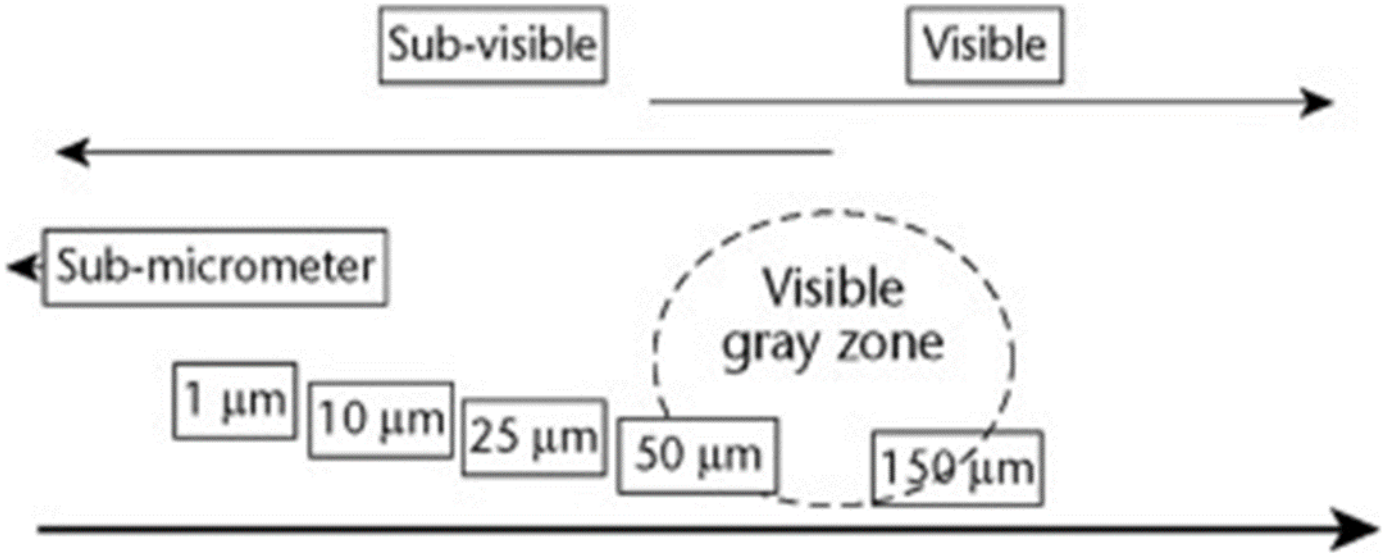
Particulate Matter

Historical Definition

Particulate matter in injections and parenteral infusions consists of extraneous mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions.

What Does That Include?

- Visible
- Subvisible



Particulate Matter Classification

Inherent

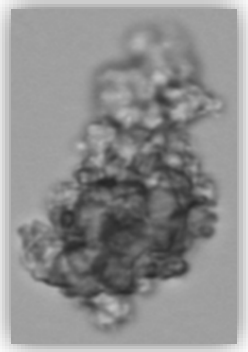
Materials that are expected from the drug substance and other formulation components, and thus represent a potentially acceptable characteristic of the product.

Source

- Part of the product

Examples

- Micro-particles
- Aggregates
- Suspension



Intrinsic

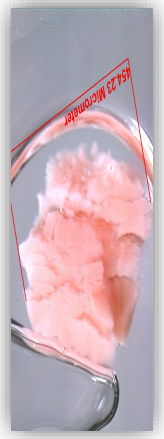
Materials occurring in the final product that arise from sources within the formulation ingredients, assembly process, or packaging.

Source

- Inside the system/process

Examples

- Packaging material
- Solution/formulation components
- Product packaging interactions
- Process generated particulates



Extrinsic

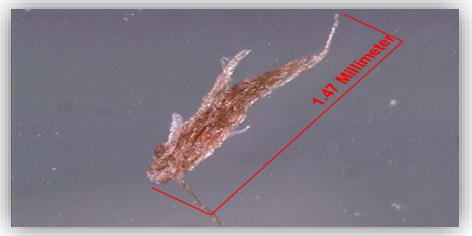
Materials that are not part of the formulation, package, or assembly process, but rather are foreign and unexpected.

Source

- Outside system/process

Examples

- Dust, paint chips, rust, insects, hairs, organic materials, fibers



1 Subvisible Particles

Subvisible Particle Chapters

<788> Particulate Matter in Injections

Year	USP Chapter	Details
1975	XIX chapter <788>	• Originally focused on extrinsic, or foreign matter, that might occlude capillaries • Membrane microscopic test for large volume injections (>100mL): NMT 50 particles/mL ≥10µm and NMT 5 particles/mL ≥25µm
1984	<788>	• LVPs use membrane microscopic and SVPs use light extinction • NMT 10,000/container ≥10µm, NMT 1,000/container ≥25µm

1995	23 <788>	• The light obscuration method is now preferred (listed as Method 1)
		  • Ease of method control, objectivity, and efficiency
		  • History of product experience and regulatory filing
		  • Membrane now “Improved Microscopic Assay” Method 2

Subvisible Chapters

Must contain low amounts of subvisible particles

Enforceable chapters

- *USP* <771> Ophthalmic Products – Quality Tests
- *USP* <787> Subvisible Particulate Matter in Therapeutic Protein Injections
- *USP* <788> Particulate Matter in Injections
- *USP* <789> Ophthalmic Solutions

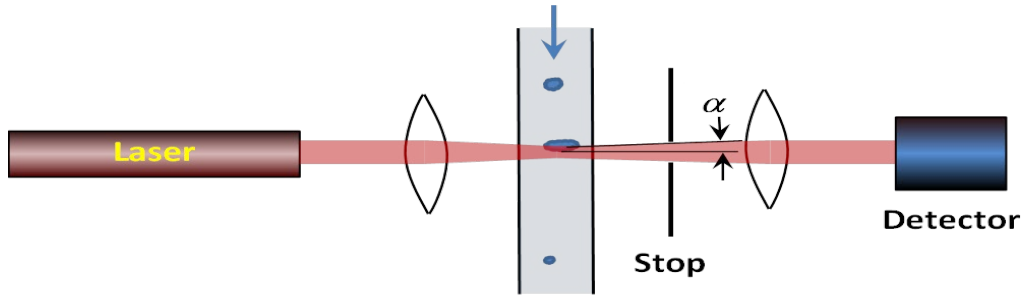
Informational chapters

- *USP* <1787> Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections
- *USP* <1788> Methods for the Determination of Subvisible Particulate Matter

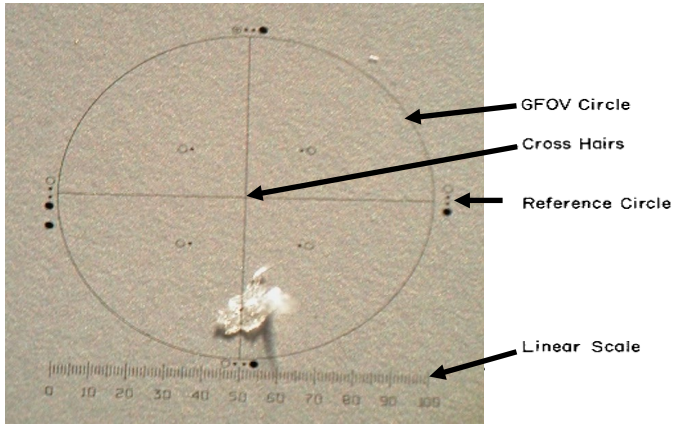
Compendial Methods

- *USP* <771> Ophthalmic Products – Quality Tests
- *USP* <787> Subvisible Particulate Matter in Therapeutic Protein Injections
- *USP* <788> Particulate Matter in Injections
- *USP* <789> Ophthalmic Solutions

Method 1: Light Obscuration Particle Count Test



Method 2: Microscopic Particle Count Test



Compendial Methods

Method 1: Light Obscuration Particle Count Test

- **Principle**
  - Uses a light-blocking technique to count and size particles.
  - Automatic measurement of particle size and number based on light blockage as particles pass through a detection chamber.
- **Apparatus**
  - Instrument calibrated with standard spherical particles (10 µm – 25 µm).
  - Particle-free water is used for calibration and testing.
- **Procedure Highlights**
  - Sample is mixed by slow inversion to avoid air bubbles.
  - The test counts particles equal to or greater than 10 µm and 25 µm.
  - Typically applied to clear solutions that do not contain air bubbles or high viscosity.
- **Application**
  - Best for solutions with good clarity.
  - Can be less suitable for viscous solutions or those that generate bubbles.

Method 2: Microscopic Particle Count Test

- **Principle**
  - Visual inspection of particles on a membrane filter after filtration.
  - Uses a microscope to manually count particles of specific sizes (≥10 µm and ≥25 µm).
- **Apparatus**
  - Binocular microscope with 100x magnification.
  - Ocular micrometer with comparison scales for 10 µm and 25 µm particles.
  - Black or dark gray membrane filter with a pore size of 1.0 µm or finer.
- **Procedure Highlights**
  - The sample is filtered through a membrane to retain particles.
  - Filter is scanned under reflected light to count particles.
  - Particles sized by comparing them with graticule reference circles on the micrometer.
- **Application**
  - Preferred for turbid or viscous solutions, or when the sample contains bubbles.
  - Can also be used when light obscuration is not feasible due to the nature of the product.

Volume Requirements and Sample Aliquots

Small-Volume Parenterals (SVP)

- **For volumes less than 25 mL**
  - **Combine** the contents of **10 or more units** into a single, cleaned container to obtain a total test volume of at least **25 mL**.
  - If necessary, mix and dilute with **particle-free water** or an appropriate solvent to reach the required volume.
- **For volumes 25 mL or more**
  - Each unit can be tested **individually** without combining multiple units.

Large-Volume Parenterals (LVP)

- **Testing Requirement:**
  - Test **single units** as individual samples without combining aliquots.
  - The entire unit is tested as it meets the required volume.

Test Aliquot Size

- **For all parenteral solutions**
  - Use a minimum of **4 portions**, each consisting of at least **5 mL** of the solution for particle counting.
  - Disregard the first portion, and calculate the mean particle count using the remaining portions.

- *USP* <771> Ophthalmic Products – Quality Tests
- *USP* <787> Subvisible Particulate Matter in Therapeutic Protein Injections
- *USP* <788> Particulate Matter in Injections
- *USP* <789> Ophthalmic Solutions

Volume Requirements and Sample Aliquots

Key Differences between <787> and <788>:

- **Volume Range:**
  - **USP <788>**: Generally, tests larger volumes (e.g., ≥25 mL for SVP).
  - **USP <787>**: Smaller volume requirements (0.2 – 5.0 mL)
- **Dilution and Pooling:**
  - **USP <787>**: Emphasizes careful dilution and pooling to avoid introducing particles, particularly for protein formulations with small volumes.
  - **USP <788>**: Generally, focuses on pooling when sample volumes are small but does not emphasize dilution procedures as much as USP <787>.
- **Mixing & Handling:**
  - **USP <788:** Sonication is used to remove air bubbles from samples in order to prevent false readings during particle counting.
  - **USP <787:** Sonication is not used due to the potential risk of protein aggregation or denaturation in sensitive therapeutic protein formulations. Instead, careful manual handling and pooling are emphasized.

- *USP* <771> Ophthalmic Products – Quality Tests
- ***USP* <787> Subvisible Particulate Matter in Therapeutic Protein Injections**
- ***USP* <788> Particulate Matter in Injections**
- *USP* <789> Ophthalmic Solutions

USP <771: Ophthalmic Products—Quality Tests

Overview

- **Purpose:**
  - Provides guidelines for the quality testing of ophthalmic products, which are sterile products intended for application to the eye.
  - Applicable to various **ophthalmic dosage forms** such as solutions, suspensions, ointments, gels, emulsions, strips, injections, inserts, and implants.

Key Ophthalmic Routes of Administration:

- **Topical** (e.g., cornea, eyelid)
- **Intraocular** (e.g., intravitreal, intracameral)
- **Extraocular** (e.g., subconjunctival, retrobulbar)

Particulate and Foreign Matter:

- **Visible and Subvisible Particulates:**
  - Testing depends on the route of administration (e.g., <788>, <789>, and <790> requirements).
  - **100% Unit Inspection** for all products to ensure the absence of unwanted particles.

Route of Administration	Must comply with USP Chapter(s)
Topical	<790>
Peribulbar	<790>, <788>
Superior rectus	<790>, <788>
Sub-Tenon	<790>, <788>
Subconjunctival	<790>, <788>
Inferior rectus	<790>, <788>
Retrobulbar	<790>, <788>
Suprachoroidal	<790>, <789>
Juxtascleral	<790>, <788>
Intrascleral	<790>, <788>
Intracorneal	<790>, <788>
Subchoroidal	<790>, <788>
Subretinal	<790>, <788>
Intracameral	<790>, <788>
Intravitreal	<790>, <788>

USP Limits for Various Sterile Dosage Forms

USP Chapter	USP Limits	Analytical
<787> Protein Injections	I: 6000 ≥ 10 µm and 600 ≥ 25 µm …data for sub-10 µm	I: Light Obscuration only
<788> Injections SVP: Per Container LVP: Per mL	I: 6000 ≥ 10 µm and 600 ≥ 25 µm II: 3000 ≥ 10 µm and 300 ≥ 25 µm I: 25 ≥ 10 µm /3 ≥ 25 µm per mL II: 12 ≥ 10 µm /2 ≥ 25 µm per mL	I: Light Obscuration II: Membrane Microscopic
<789> Ophthalmic Solutions Per mL	I and II: 50 ≥ 10 µm 5 ≥ 25 µm 2 ≥ 50 µm	I: Light Obscuration II: Membrane Microscopic
<771> Ophthalmic Products	100% inspection for package and fill defects	Use <788> for extra-, <789> for inter-ocular administration

Subvisible Particulate Matter in Injections

2014

<787> Subvisible Particulate Matter in Therapeutic Protein Injections

- Chapter was developed as an alternative to *USP* general chapter *Particulate Matter in Injections* <788>.
- Meant to specifically addresses therapeutic protein injections and related preparations, allowing use of:
  - Smaller test product volumes
  - Smaller test aliquots to determine particulate matter content
  - Sample-handling instructions that take into account the issues associated with the analysis of these materials.

2021

- Proposal to omit chapter from the USP-NF

2021

<788> Particulate Matter in Injections (*PDG harmonized*)

- Meant to specifically addresses therapeutic protein injections and related preparations, allowing use of:
  - Single-unit testing for both large- and small-volume parenterals
  - Smaller test aliquots to determine particulate matter content
  - Easy sample preparation of protein products
  - Sample-handling instructions that take into account the issues associated with the analysis of these materials.

2024

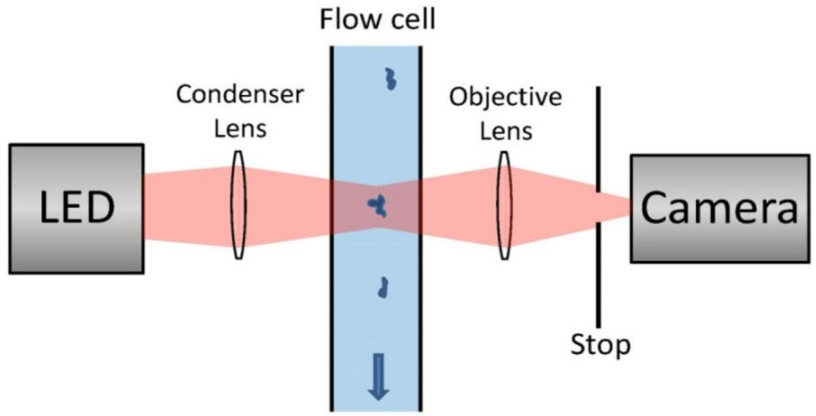
- Current harmonization conversations with JP and EP to finalize.

Informational Subvisible Particle Chapters

- **<1787> Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections** (effective 2015)
  - Informational chapter covering available methods for SbVP analysis and their strengths and weaknesses
  - Includes discussion on applications of analyses during development lifecycle
- **<1788> Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions** (published 2011, revised 2021)
  - Informational chapter focusing on applications and development of light obscuration, flow imaging, and membrane microscopic methods
  - Includes best practices for qualification, etc.
  - Expanded:
    - ⟨1788.1⟩ Light Obscuration Method for the Determination of Subvisible Particulate Matter
    - ⟨1788.2⟩ Membrane Microscope Method for the Determination of Subvisible Particulate Matter
    - ⟨1788.3⟩ Flow Imaging Method for the Determination of Subvisible Particulate Matter

Flow Imaging

While sample passes through flow cell, a microscope images particles & analyzes data automatically



Advantages

- Analysis of images enables identification of particle type (e.g., silicone oil vs. protein aggregate)
- Ease of use improving
- Extremely high dynamic range for particle count (10 mL^{-1} to 10^6 mL^{-1})

Disadvantages

- Optical resolution limited to 2 µm
- > 0.2 mL volume per measurement

USP <1787>: Methods for Subvisible Particle Measurement

Method	Phase	Comments
Backgrounded Membrane Imaging (BMI)	Development and Characterization	Similar to membrane microscopy, with automation and particle differentiation; small sample volume
Light Obscuration (LO)	Characterization and Lot release	Robust, but no specificity and sensitive to particle optical contrast
Dynamic Imaging (Flow Microscopy) (DIA, FI, FM)	Characterization, possibly lot release	Lower throughput and not as robust, but better specificity, dynamic range, and not as sensitive to optical contrast
Electrical Sensing Zone (ESZ)	Characterization	Non-optical technique, for samples unsuited for optical counting; no specificity
FTIR & Raman Microscopy	Characterization and Root Cause	ID particle type and protein conformation; very low throughput
Fluorescence Microscopy	Characterization and Root Cause	ID particle type and protein conformation; very low throughput
SEM-EDX	Root Cause	ID particle type; very low throughput

Note: BMI is a recent method and not in <1787>

USP <1787> Methods for < 2µm

Method	Phase	Comments
Analytical ultra-centrifugation (AUC)	Characterization	Qualification of Size Exclusion Chromatography
Field flow fractionation (FFF)	Characterization	Useful method of separating by size; used with multiple detection schemes
Electrical sensing zone/Resistance pulse sensing (RPS)	Characterization	Non-optical technique, for samples unsuited for optical counting
Light obscuration/scattering	Characterization	Extension of LO to lower sizes by light scattering
Static light scattering	Characterization	Straightforward measurement, but need to assess ability to span full size range of interest
Nanoparticle tracking analysis (NTA)	Characterization	Workhorse technique, but may be sensitive to instrument settings
Resonant mass measurement (RMM) / Suspended microchannel resonator (SMR)	Characterization	Orthogonal technique to distinguish silicone from non-silicone, but commercial instrument no longer sold
Flow cytometry	Characterization & Root Cause	Capable of distinguishing particle type by scattering and fluorescence labeling
Atomic force microscopy (AFM) & Electron microscopy	Characterization & Root Cause	ID particle type; very low throughput
Turbidity/Nephelometry	Characterization; Lot release	Simple technique, but only a relative measure of particle load

Concerns about Silicone Oil: Analytical

- Silicone oil is identified as a particle by most techniques that are currently used for subvisible and visible particle assessment
  - The presence of silicone oil can increase a product's particle counts above the compendial limits
  - High silicone oil background can confound an organization's ability to track changes in foreign, or other, particles.

Thank You

The standard of trust

INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

Evaluating Clinical and Analytical Impact of Subvisible Silicone Oil Particles in Biopharmaceutical Products

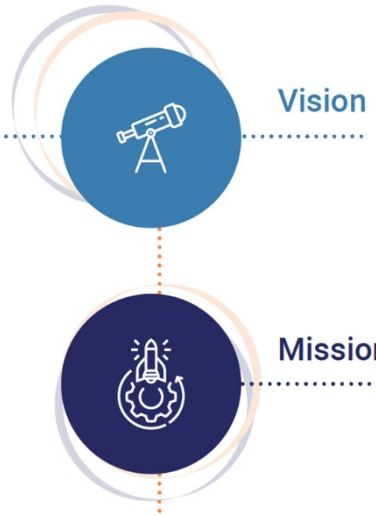
Miguel Saggu

USP/IQ Consortium Roundtable

07-Oct-2024

INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium) was established in 2010 as a technically-focused, not-for-profit organization comprised of nearly 40 pharmaceutical and biotechnology companies.

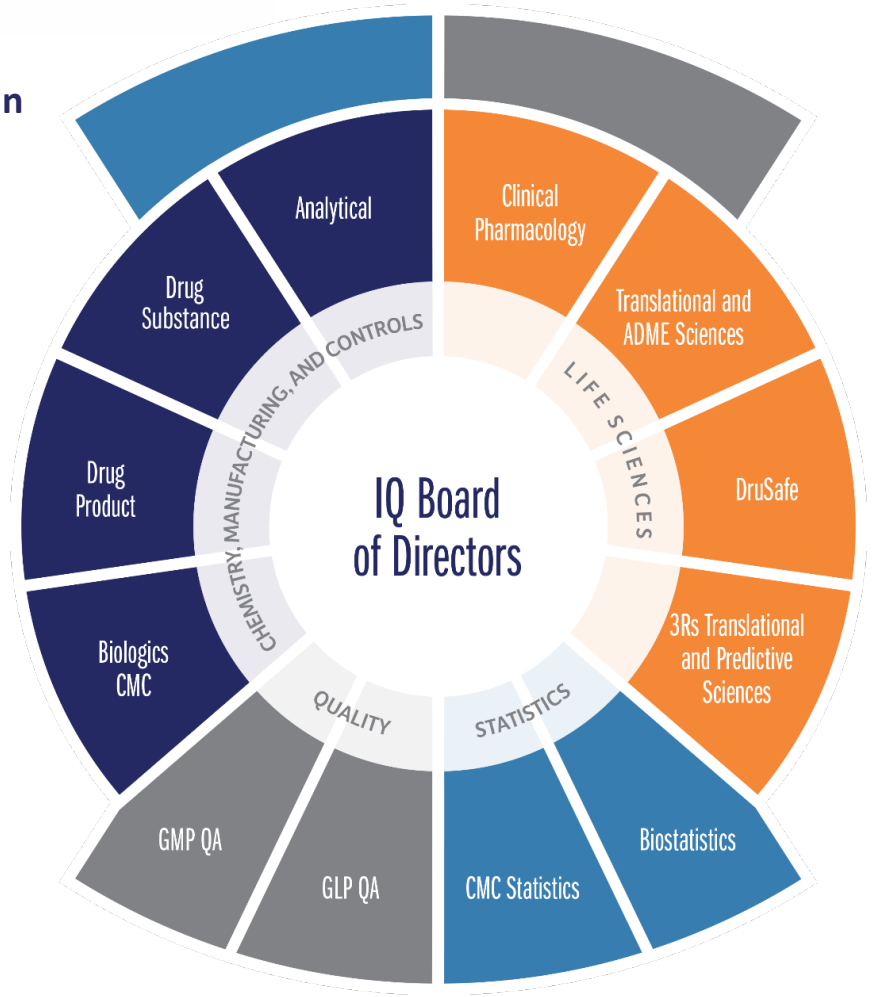


Vision

To be the leading science-based organization advancing innovative solutions to biomedical problems and enabling pharmaceutical companies to bring quality medicines to patients.

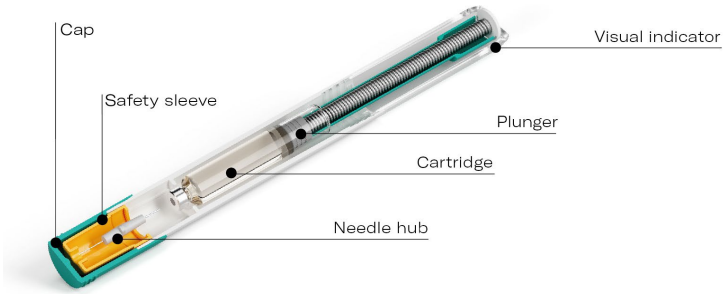
Mission

As a technically-focused organization of pharmaceutical and biotechnology companies**, IQ advances science and technology** to augment the capability of member companies to bring transformational solutions that benefit patients, regulators and the broader R&D community.



https://iqconsortium.org

Pre-filled Syringes (PFS) and Autoinjectors



Advantages

- Lack of compounding
- End-user convenience, e.g. home administration
- Ease of handling

Silicone oil is used as a lubricant to facilitate plunger gliding but it can migrate into the drug product solution solution

Challenges

1. Analytical: Presence of silicone oil droplets/particles (SiOPs) can complicate quantitation and characterization of other types of SVPs in solution
2. Clinical: SiOPs could potentially present safety risks for patients

Variability of Silicone Oil Migration into Solution

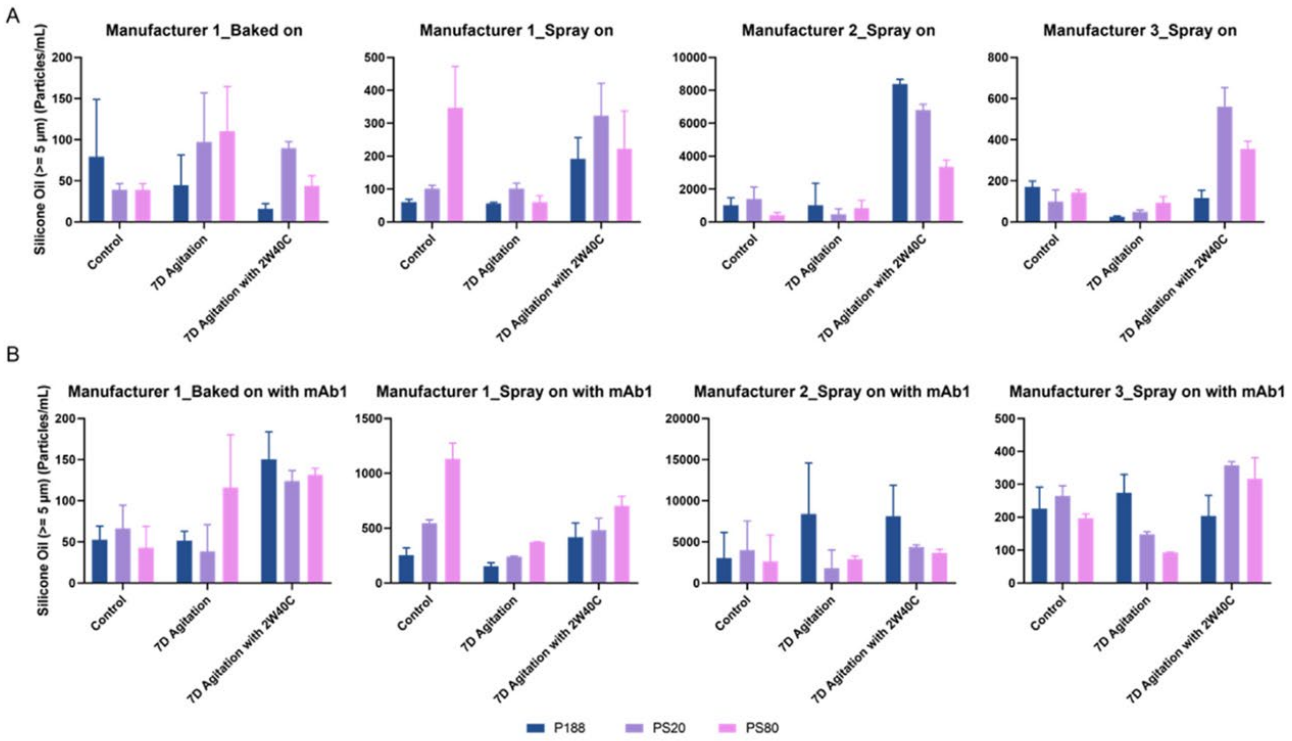


Fig. 4. MFI results of silicone oil ($\geq 5\mu m$) particle counts in the absence of protein (A) and presence of protein (B) with 0.02% (w/v) P188, PS20 and PS80, respectively, under control, mechanical stress, and combination stresses.

Gentile et al., J. Pharm. Sci. (2023)

Silicone oil Can Act As Adjuvant At Very High Concentrations

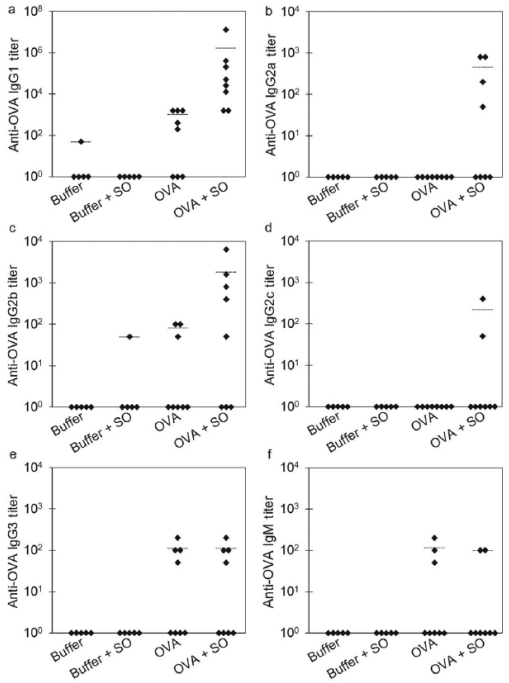
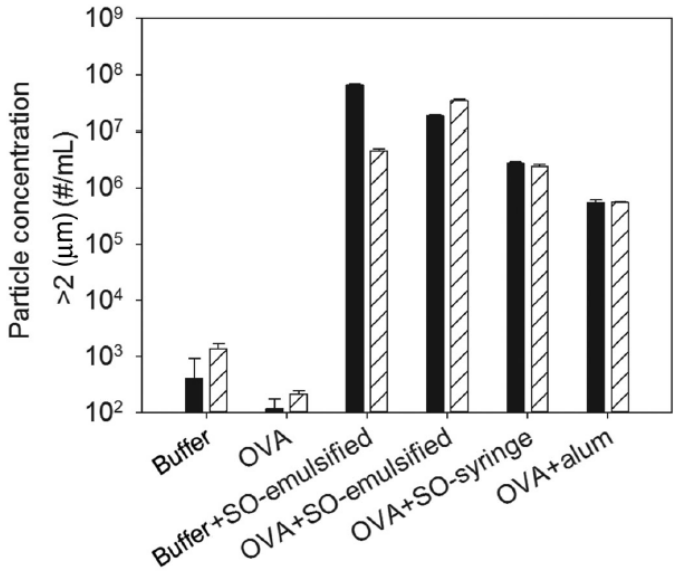


Figure 4. Anti-OVA antibody titers for mice treated with formulations of buffer, buffer that contained emulsified silicone oil microdroplets, OVA, and OVA that contained emulsified silicone oil microdroplets at day 29 for IgG1 isotype (a), IgG2a isotype (b), IgG2b isotype (c), IgG2c isotype (d), IgG3 isotype (e), and IgM isotype (f). Each data point represents the titer value of an individual mouse. Bars represent the average titer of mice that responded within that group.



Chisholm et al., J. Pharm. Sci. (2015)

Si Oil Task Force

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Objective

“Evaluating Clinical Safety and Analytical Impact of Subvisible Silicone Particles on Biotherapeutic Products”

1. Collect/utilize data and provide case studies from multiple organizations and different biotherapeutics to evaluate whether silicone oil droplets might present safety concerns (or not) and may even be justifiable above current USP<788> SVP limits (e.g. for novel modalities, if no product quality impact)
    - Discussion will address quality impact raised by prior academic groups (e.g. silicone oil induced protein aggregation in the absence of detergent).
    - Discussion will also address potential silicone oil induced immunogenicity concern shown in prior publications
2. Analytical impact due to the presence of silicone oil and how to ameliorate these challenges
    - Discussion will address various analytical techniques/algorithms used and their ability for differentiating silicone oil from other types of particles

Case Studies

Eight case studies in total (3 analytical case studies and 5 clinical case studies)

- Includes data of different formats including mAbs, bispecific and smaller biologics
- The patient populations cover multiple groups including autoimmune, metabolic disorder, etc.
- No pre-/biased selection based on safety profile of the drugs

1. Analytical Case Studies

- Comparison of subvisible particle levels in vial presentation vs. PFS
- Discussion about impact on other product quality attributes due to the presence of silicone oil, e.g. aggregates, potency, etc.

2. Clinical Case Studies

- Safety comparison of different formats in vial vs. PFS
- Includes data about immunogenicity, injection site reactions etc.

Published in J. Pharm. Sci. (2024)
DOI: https://doi.org/10.1016/j.xphs.2024.01.002

Toxicology of Silicone Oil

EVALUATION

Level causing no toxicological effect

Rat: 0.1% (= 1000 ppm) in the diet equivalent to 150 mg/kg bw

Estimate of acceptable daily intake for man

0–1.5 mg/kg bw

- WHO Food Additives Series, WHO 1975

For other routes of administration such as intravenous (IV) can assume a safety factor, e.g. 10x, resulting in daily limit of 150 µg/kg PDMS (silicone oil)

Examples

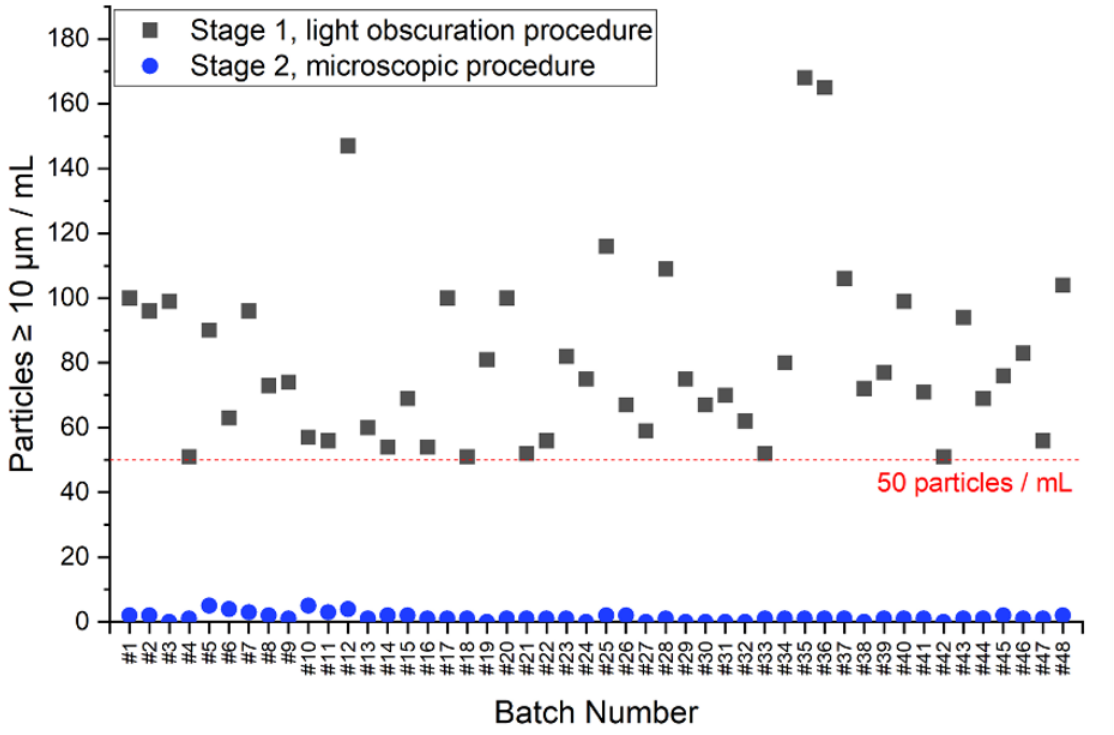
- Typically, in PFS the amount of PDMS in solution is in the low µg/mL range
- Total siliconization of a PFS is typically below 1 mg/PFS
- In conclusion, the level of PDMS in PFS is well below the toxicological limit

Case Study 1 - Ocular Product in Vial vs. PFS

- Compound A is a protein for intravitreal injection
- There was a format change from vial to PFS
- Must comply with USP<789> specifications for SVPs

Size range	USP<789> Acceptance criteria limits for ophthalmic solutions Stage 1 & 2 testing
≥ 10 µm	50 particles / mL
≥ 25 µm	5 particles / mL
≥ 50 µm	2 particles / mL

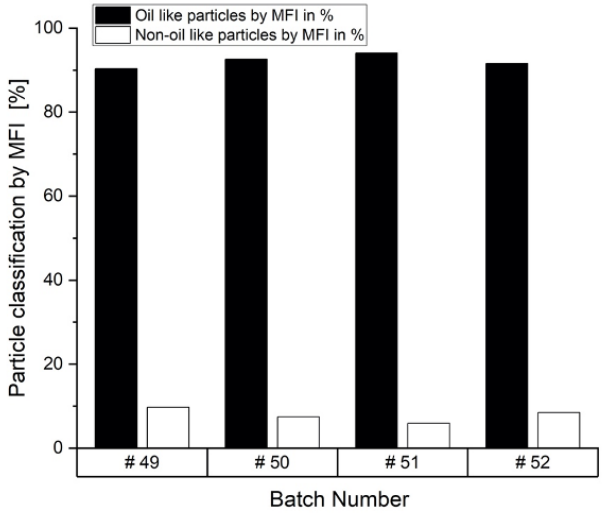
Case Study 1 - Batch Overview



- Out of 144 produced batches 48 failed stage 1 SVP testing by LO
  - 47 failed limits for particles ≥10 µm and 1 failed limits ≥50 µm
- All batches passed stage 2 SVP testing by membrane microscopy as the silicone oil droplets are filtered through the membrane

Case Study 1 - Dynamic Flow Imaging

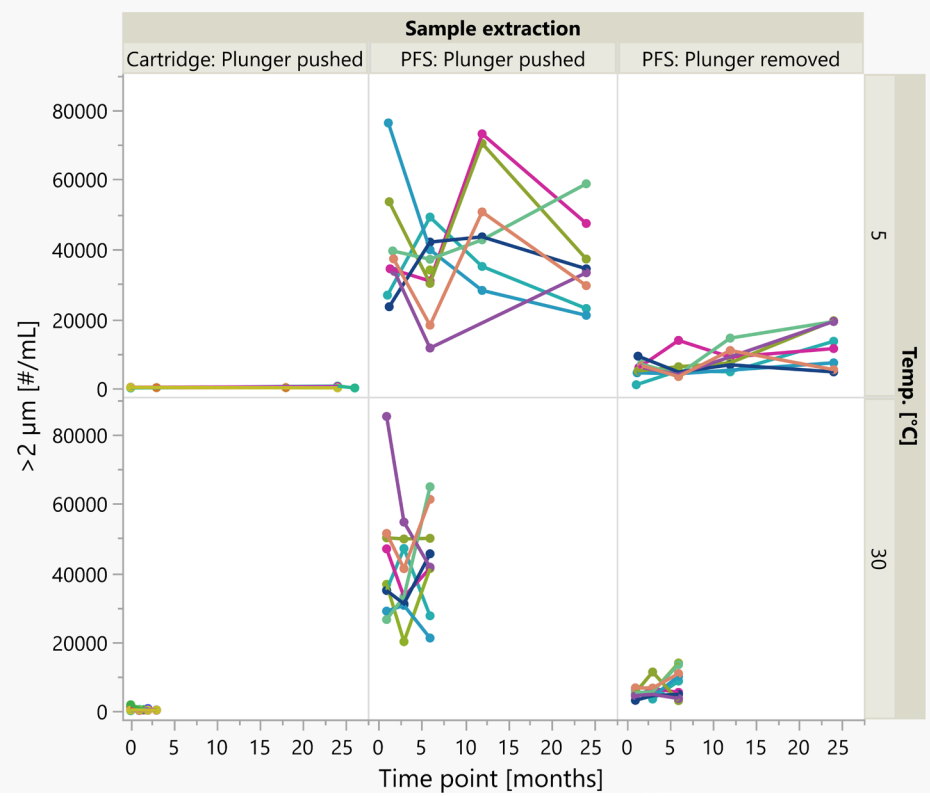
Batch	Particles ≥5 µm [/mL]	Particles ≥10 µm [/mL]	Particles ≥25 µm [/mL]	SiOP ≥5 µm [%]	Non- SiOP ≥5 µm [%]
#49	2109	127	2	90.3	9.7
#50	1312	72	5	92.6	7.4
#51	1801	96	2	94.0	6.0
#52	1944	91	11	91.5	8.5



- The level of silicone oil present in drug product solution derived from PFS is in the same range as the amount of silicone oil in drug product solution derived from a vial presentation after administration using disposable syringes (data not shown).
- Silicone oil itself as well as silicone oil particles/droplets are regarded as non-critical/ non-toxic material and therefore their well understood content is considered acceptable.

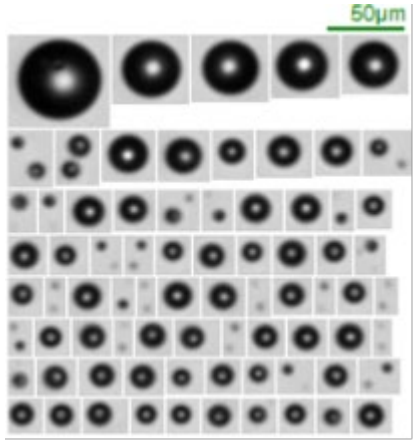
Case Study 2 - Compound B in Cartridge vs. PFS

- Multi-use cartridge with baked-on silicone oil
- Single-use PFS with sprayed-on silicone oil



Sub-visible particle counts (≥ 2 µm) by MFI for 12 production scale batches filled in cartridges (plunger pushed) and for nine New Drug Application (NDA) batches filled in PFS

Silicone oil shedding into solution upon dosing from PFS



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Case Study 2 - Other Attributes

- Impurity profiles and and amount of aggregates (by size-exclusion chromatography) were comparable between the two configurations
- Only observed difference was SVP levels
- ~10 ug PDMS is getting shed into solution during dosing from PFS (~1 ug PDMS from cartridge) as quantified by ^{1}H-NMR

Clinical safety

- Data from clinical trials showed no difference in the proportion of anti-drug antibody (ADA) positive subjects in the PFS treatment group (1% of around 400 patients) versus the cartridge group (1-2% of more than 2000 patients)
- A predefined MedDRA search was performed to identify all adverse events (AEs) of injection site reactions in the clinical trials for subjects treated with PFS. The evaluation was based on the on-treatment period. AEs of injection site reactions were reported by few subjects in all treatment groups. These events were reported by a comparable proportion of subjects in each treatment group and with a similar or lower event rate than placebo.
    - The most frequently reported preferred terms (PTs) were injection site pain and injection site bruising. All reported events were non-serious and mainly mild or moderate in severity.

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Case Study 3 – mAb in Vial vs. PFS

- mAb-X is a humanized IgG1.
- The PFS is administered bi-weekly SC while the IV infusion is administered every 4 weeks.
- The particle counts/container ≥10 µm were in the range between 50-300 and for particles ≥25 µm between 0-20 for both IV and SC configuration. It should be noted that the fill volume is larger (and the API concentration lower) for the vial (particles/mL much lower).
- Additional Polydimethylsiloxane (PDMS) quantification in solution of the SC configuration during shelf-life showed that typical values are between 2-10 µg/mL PDMS/container.

Clinical data

The global safety database contains information from clinical trials, spontaneous reports as well as reports from non-interventional studies and programs, registries and literature.

1. Comparison of cumulative events of IV vs SC (all events)
2. Analysis of pre-defined events possibly related to product issues

Comparison of Cumulative Events of IV vs. SC Treatment with mAb-X

	Cumulative IV mAb-X (control)		Cumulative SC mAb-X	
Exposure Number of Patients	**668,594**		**176,344**	
Patient years (PY)	**541,668**		**142,790**	
SOC Name	**# Events**	**Reporting Rate /100 PY**	**# Events**	**Reporting Rate /100 PY**
Immune system disorders	1959	0.29	381	0.22
Vascular disorders	4271	0.64	475	0.27
Skin and Subcutaneous tissue disorders	9092	1.36	2438	1.38

- Only patients exclusively dosed IV or SC
- No difference in safety profile observed

Comparison of Cumulative Reporting Rates of Other Events Potentially Indicating Product Quality Issues

HGLT Procedural related injuries and complications NEC	**Cumulative Reporting Rate IV mAb-X (control)**	**Cumulative Reporting Rate SC mAb-X**
PT Infusion related reaction	0.24%	0.01%
PT Injection related reaction	0.00%	0.01%
HGLT Allergic Conditions	**Cumulative Reporting Rate IV mAb-X (control)**	**Cumulative Reporting Rate SC mAb-X**
PT Hypersensitivity	0.11%	0.11%
PT Drug Hypersensitivity	0.03%	0.04%
PT Anaphylactic Reaction	0.05%	0.01%
PT Anaphylactic Shock	0.02%	0.00%

Summary

- The case studies demonstrate that techniques such as dynamic flow imaging, ^{1}H-NMR, and other assays for amount of PDMS can be used to determine differences in silicone oil content and contribution to the particle population as changes in formulation and administration device/method occur and are valuable tools during product development
- One observation was that it is critical to control the method by which the solution is removed from the PFS. As demonstrated in one case study, removing the plunger and decanting the DP from the PFS results in less silicone oil (fewer droplets) than expelling the DP from the syringe in the method used for administration to patients. In order to mimic what patient exposure is it is critical to remove DP from devices as if it is being administered.
- There was no detectable impact on injection site reactions or immunogenicity of a DP with increased silicone oil particles or content across a range of patient populations.
- Conflicting results on the effect of increased silicone oil particles on the immunogenicity of protein therapeutics were described in previous publications. This could be because of differences in the model systems used, in the preparation of the silicone oil droplets, incubation of model DP in the devices with the increased silicone oil, etc.
    - The actual clinical impact of potential CQAs can only be assessed from patients in a clinical setting (e.g. clinical data from case study 3)

Acknowledgement

This presentation was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, www.iqconsortium.org). IQ is a not-for-profit organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader research and development community.

U.S. FOOD & DRUG ADMINISTRATION

Silicone Oil Particle Analytics

Ashwinkumar Bhirde, Ph.D.
Senior Research Scientist

USP/IQ Consortium Roundtable: Subvisible Silicone Oil Droplets on Particle Analysis
10-07-2024

Division of Pharmaceutical Quality Research VI (DPQRVI)
Office of Pharmaceutical Quality Research (OPQR), OPQ/CDER/U.S. FDA

Disclaimer:

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Everyone deserves confidence
in their *next* dose of medicine.

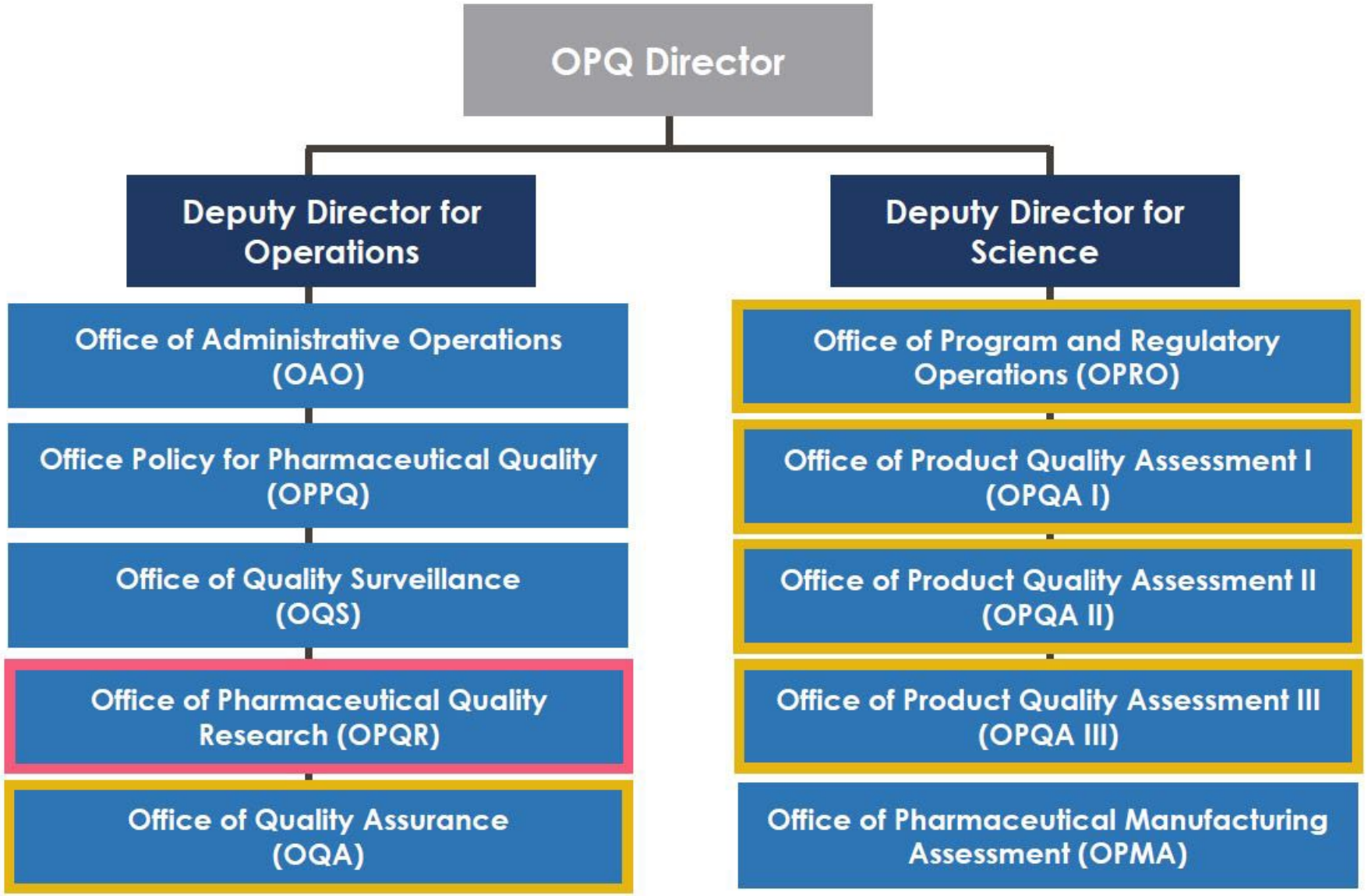
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

www.fda.gov

Outline

1. Drug Product recalls due to Particulates
2. Regulations
3. Case Studies
4. Regulatory Research

Office of Pharmaceutical Quality (OPQ)



What are Particulates?

USP<788> Particulate Matter Definition

Extraneous mobile undissolved particles, other than gas bubbles, unintentionally present in solutions

CQA Definition (ICH Q8(R2))

A critical quality attribute (CQA) is defined by the ICH as a physical, chemical, biological, or microbiological property or characteristic of an output material including finished drug product that should be within an appropriate limit, range, or distribution to ensure the desired product quality

USP <787> Subvisible Particulate Matter In Therapeutic Protein Injections Particles:

Extrinsic - unexpected foreign material (e.g., cellulose)

Intrinsic - resulting from addition or by insufficient cleaning during manufacturing (e.g., tank metals or insoluble salt forms)

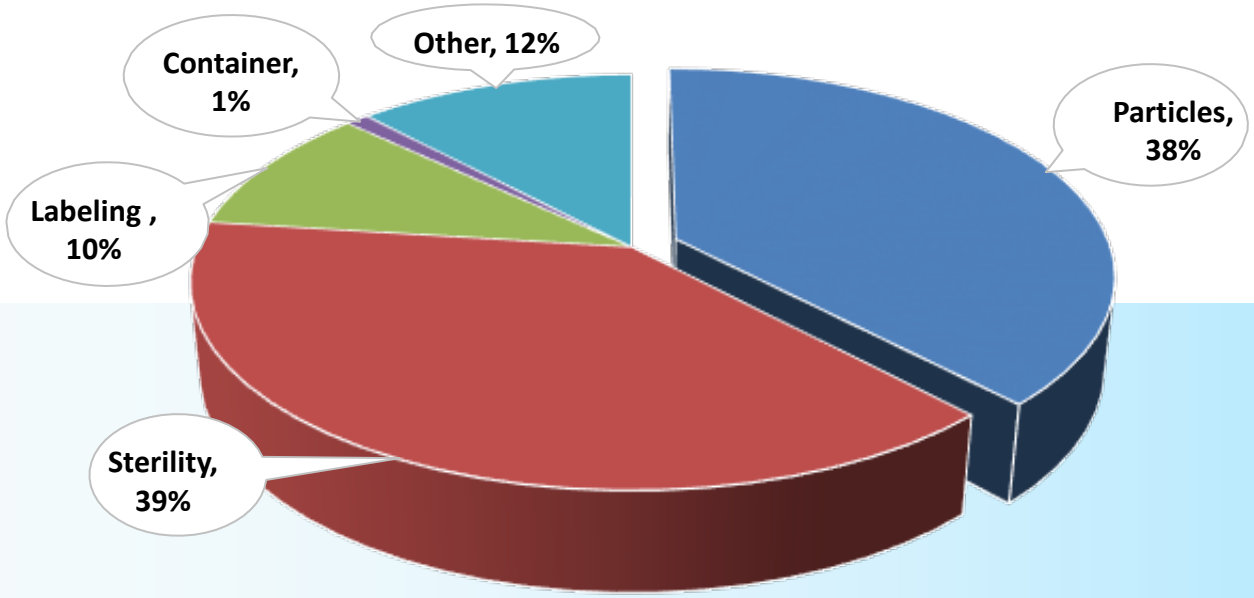
Inherent - particles of the protein or formulation components

*Ashwinkumar Bhirde 2022 AAPS NBC, Anaheim, California, USA

Drug Product Recalls due to Particulates

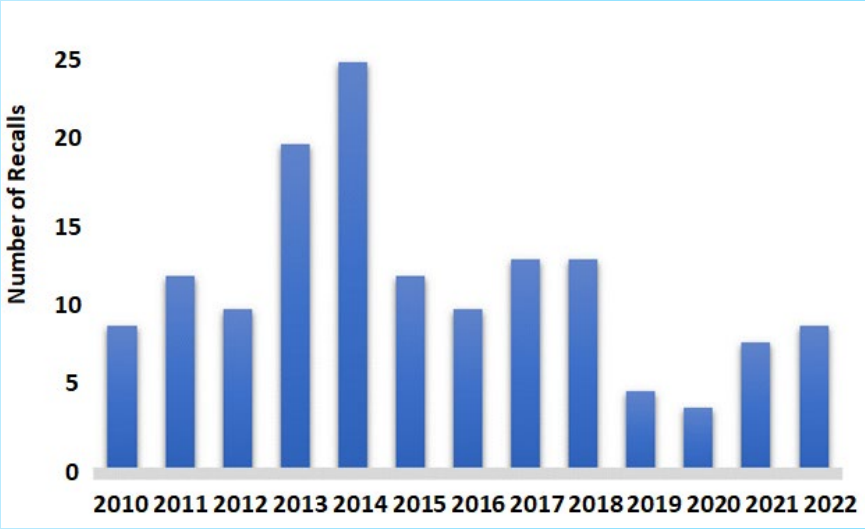
- Particulates: Can impact Quality, Safety, Efficacy and Pharmacokinetics of a Drug Product.

Recall Notices in Injectable Products:



2015 - 2019

Product Recalls Due to Particulates



*Ashwinkumar Bhirde 2022 AAPS NBC, Anaheim, California, USA

Regulatory Expectations During Early Phase Development

- Extended characterization to assess particulate formation to understand the CQAs
- Characterization of particulates at release, stability and in-use conditions
- Strategies should be implemented to minimize formation of particulates
- Methods with enhanced detection of particulates to characterize distinct species of aggregates
- If particulates are observed, a risk assessment should be performed to understand the impact of particulates on the clinical performance of the product and develop control strategies to mitigate the risk

Regulatory Expectations During Phase 3 Studies

- Particulate analysis should be part of overall product characterization including a risk assessment of their potential impact on safety and efficacy
- Multiple stress conditions to assess the propensity to form particulates and evaluate stability indicating properties of assays
- If unusual trend of increasing particulates is observed during storage, investigation should be performed to identify the root cause
- Orthogonal methods with different separation and detection principle should be used to characterize the physiochemical properties of particulates such as size shape and composition

Regulatory Expectations At Licensure

- Particulates acceptance criteria should be based on clinical and pre-clinical experience with consideration for manufacturing experience and immunogenicity risk
- The analytical methods should be validated or qualified for their ability to detect and quantify particulates
- Particulates type (proteinaceous, silicon oil etc.), shape (globular or filamentous), size distribution including images should be provided

USP Testing for Particulate Matter

SVP	Visible
USP<788>, <787> and <789> -DP release and stability specifications for ≥ 10 µm and ≥ 25 µm -Methods: LO and MM - Allows use of alternative analytical methods	USP<1> and <790> -DP should be 100% visual inspected for foreign particulate matter -Visible particulate specification should be incorporated into the DS and DP release and stability programs
USP <1787> • Recommends the collection of 2-10 µm SVP • Orthogonal methods to characterize SVP • Recommendation to distinguish silicon oil from other proteinaceous, inherent or intrinsic particles	

Regulatory Guidance

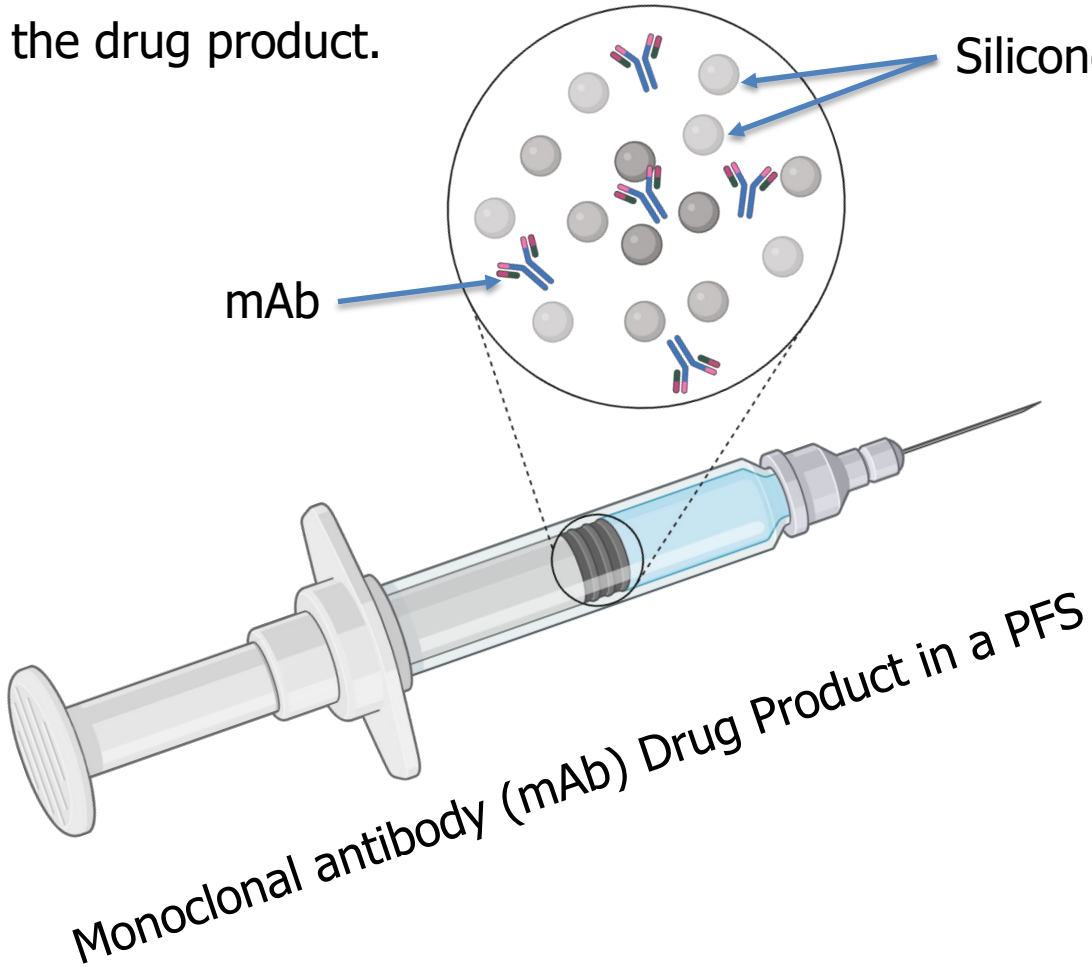
FDA Guidance	
Guidance for Industry "Immunogenicity Assessment for Therapeutic Protein Products"	
Guidance for Industry "Inspection of Injectable Products for Visible Particulates"	
ICH Guidance	
Q7	Provide guidance regarding cGMP for the manufacturing of API under an appropriate system for managing quality
Q8	Pharmaceutical development – "design a quality product and its manufacturing process to consistently deliver the intended performance of the product" CCS - "The choice of materials for primary packaging should be justified… A possible interaction between product and container or label should be considered"
Q9	Quality risk management - identifying which material attributes and process parameters potentially have an effect on product CQAs
Q10	Pharmaceutical quality system– provides enhanced assurance of product quality throughout the product lifecycle

*Rukman De Silva 2021 PDA Visual Inspection Forum

Silicone Oil particles – Case Studies

- Silicone oil is added to the syringe manufacturing process to ensure the plunger can easily glide down the barrel.

- Silicone oil particles can leach into the drug product.



Case Study 1 (mAb DP in PFS (Type I borosilicate glass syringe))

- Assessment of compatibility of the unbuffered formulation with the approved syringe 1 with higher silicone levels and the proposed syringe 2 with lower silicone levels showed similar results for most product quality attributes, except lower silicone particulates. Extractables and leachables studies for the new CCS, including under long term storage conditions, supported low levels of leachables within safety limits, including silicone.

- Flow imaging analysis was more sensitive than light obscuration and allowed for differentiation of circular species (including silicone oil) at ≥5 µm. CCS 2 showed a higher level of particulate matter at the accelerated temperature condition that is not likely related to the process variables studied, but more attributable to variability of particulate matter present from silicone dislodged from the syringe barrel.

- Higher number of subvisible particles in the ≥2 µm and ≥5 µm size ranges were identified in the unbuffered compared to the buffered formulation. Characterization of these particles showed that majority of the particles were of silicone oil inherent to the CCS. This was the reason the Sponsor changed the CCS.

- The results showed an increase in circular particulates at the accelerated temperatures that indicated the particulate count increase was largely due to dispersion of silicone oil in the formulation.

Case Study 1 (mAb DP in PFS (Type I borosilicate glass syringe))

- The higher 10 and 25 micron particulate matter results in the unbuffered DP at elevated temperatures and all temperatures for all smaller size particulates (<10 micron) were attributed to higher levels of silicone in DP. The higher levels of silicone/silicone particulates in DP did not appear to impact DP stability because the stability profiles for other DP quality attributes were comparable.

- The Sponsor hypothesized that the subvisible particulates were silicone oil from the syringe barrel. The changes in formulation composition, relative to the current commercial formulation, appears to promote the migration of the silicone oil from the syringe surface into the bulk DP solution, which manifested as circular subvisible particles detected by the assays. According to the Sponsor due to oil migration, the lubricity of the syringe got decreased and subsequently the glide force required to expel the DP increased.

- Silicone was the only leachable that had concentration above reporting limit. The reported silicone concentration (3.63 mcg/mL) was well below the acceptable daily intake (1200 mcg) and hence it was not of toxicological concern.

Case Study 2 (G-CSF DP in PFS)

- To support compatibility of G-CSF DP with the prefilled syringe container closure system, sponsor provided leachables data for the syringe 1 and syringe 2 stored at the recommended storage condition of 2-8˚C. Sponsor considered syringe 2 as worst-case scenario with respect to leachables because of its higher silicone oil content. The sponsor was asked to monitor syringe 2 until the proposed expiry, provide updated leachables data stored up to the end of shelf life at the proposed long-term storage conditions .

- The data from the spiking studies suggested that silicone oil levels in the syringe 1and syringe 2 were compatible with G-CSF DP . In addition, the Sponsor acknowledged that silicone could interact with proteins to form aggregates. The MFI results showed an increase in subvisible particles in the silicone oil spiking study, which the Sponsor attributed to silicone oil particles that were not related to product stability.

- Visual inspection, MFI analysis, protein concentration, pH, CEX-HPLC, SECHPLC, and RP-HPLC analytical techniques were used to monitor any particles or aggregate formation and other changes in product quality over time.

Case Study 3 (mAb DP in PFS (Type I borosilicate glass syringe))

- Silicone oil particles and other particles were detected by flow imaging. The great majority of the sub-visible particles at all the testing time points for all three configurations were silicone oil droplets, which was used for coating of the internal surface of the syringes and stoppers. Solution for injection in pre-filled syringe (PFS) with needle safety device (NSD) and mAb 300 mg/2.0 mL Solution for injection in PFS in autoinjector (AI), compared with the bulk PFS.

Batch	Pull Point (months)*	Silicone Oil droplets (%)**	Other particles (%)**
Bulk PFS	T0 (release)	95.3	3.5
	1	99.5	0.5
	3	92.2	7.8
	6	92.6	7.4
PFS-AI	T0 (release)	97.1	2.9
	1	98.6	1.4
	3	98.0	2.2
	6	99.1	0.9
PFS-NSD	T0 (release)	99.7	0.4
	1	100.0	0.0
	3	99.5	0.5
	6	98.6	1.4

*storage under intended conditions (2-8 ^{o}C)

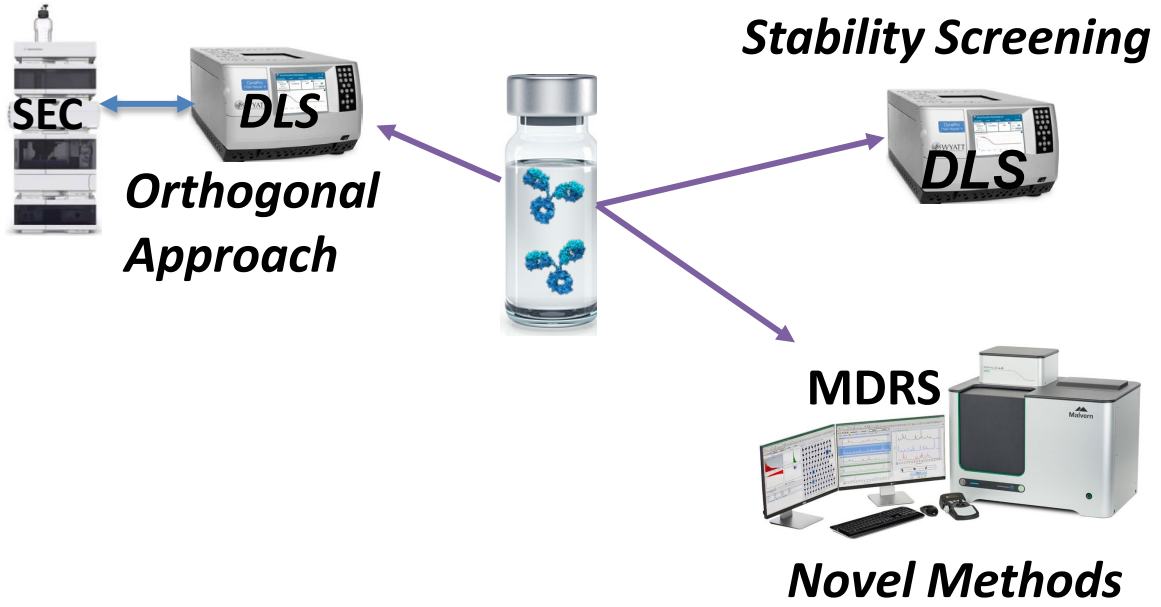
** percentage of overall detected subvisible particles ≥ 10 µm determined by MFI. Minor differences to 100% for the sum of silicone oil droplets and other particles are due to rounding

Advanced Characterizations of Biologics Team Complex Product Characterization Group (DPQRVI)

Our Expertise: We evaluate critical quality attributes (CQA) that impact the drug product quality during and after manufacturing. CQA's evaluated are purity, high molecular weight species (HMWS) particulate formation, aggregation, analytical comparability for biosimilars, stability studies (real-time and stressed stability) of the biologic drug products.

Research Objectives:

1. Method development to address gaps
2. Provide reviewers with relevant information to make science-based review decision
3. Help revise recommended review practices
4. Aid in developing safe and effective drugs



**DP = Drug Product*

Biologic DP Quality Research – DPQRVI (Instrumentation)

FDA

- Lab research conducted provided the scientific background to be an SME in particulate detection, characterization, quantitation, classification and identification.

Our capabilities to evaluate the CQA of the biologic drug product include:

←Monomer/HMWS → ← Subvisible particulates ← Visible particulates →

HPLC

DLS

FlowCam Nano

FlowCam LO

Morphology 4ID

Junior Biologics

Surface Charge

Thermal Stability

Current research:

- Evaluation of critical quality attributes like particulate formation, and aggregation
- Stability studies that impact quality of biologics during and after manufacturing
- Analytical comparability for biosimilars
- Stability of biologic drugs in various container closure systems
- Testing of novel reference standard materials

DP = Drug Product

Container Closure System: Drug-Device Combination Products

Vials, Pens, Pumps, Syringes – Ongoing

FlowCam LO

DLS

MDRS

scientific reports

OPEN

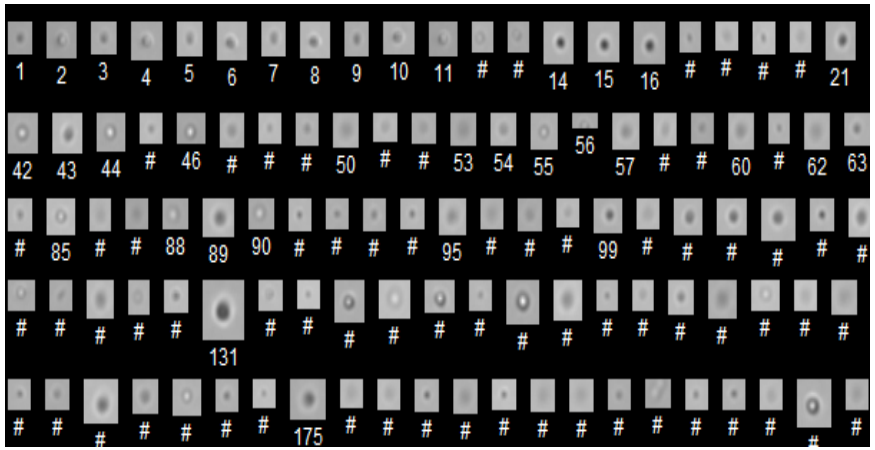
Morphologically-Directed Raman Spectroscopy as an Analytical Method for Subvisible Particle Characterization in Therapeutic Protein Product Quality

Minkyung Kim[1], Youlong Ma[2], Charudharshini Srinivasan[2], Thomas O'Connor[2], Srivalli N. Telikepalli[3], Dean C. Ripple[3], Scott Lute[1]✉ & Ashwinkumar Bhirde[1]✉

*Sci Rep. 2023 Nov 22;13(1):20473.

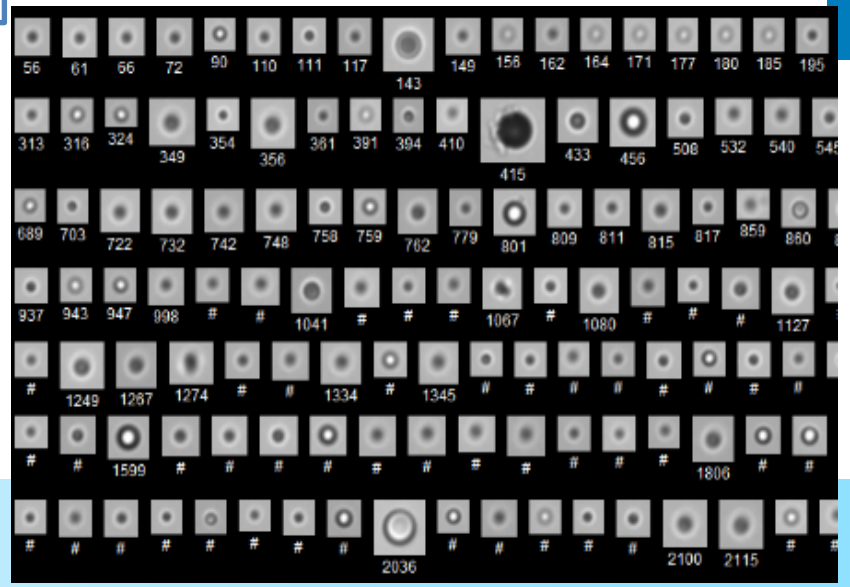
Biologic DP Quality Research (Subvisible Particulate Detection)

Apidra Vial Control

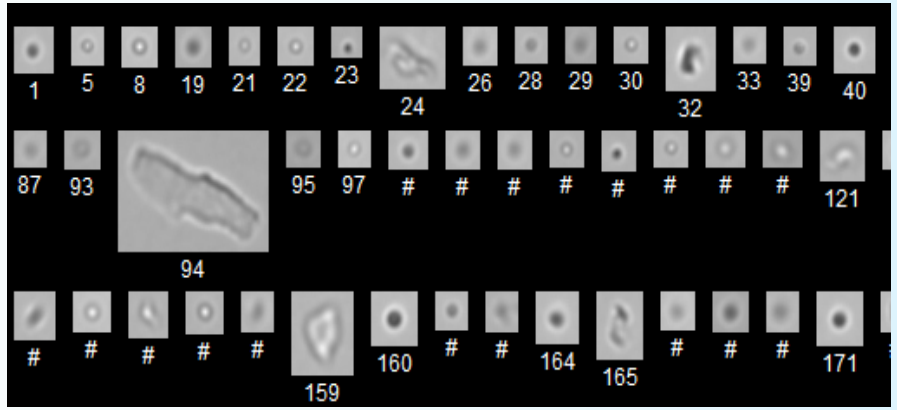


Flow Imaging Method

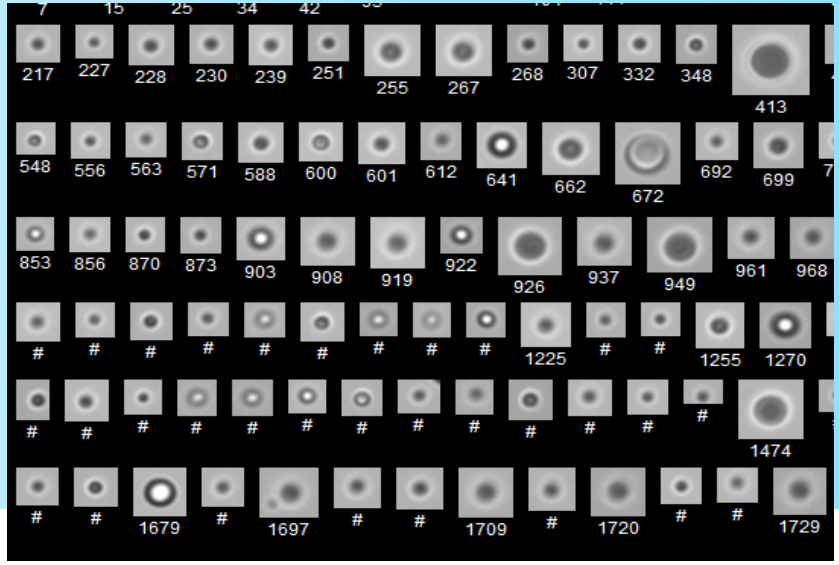
Apidra Pen Control



Apidra Vial Stressed (Agitation) 300 rpm 3 hrs.

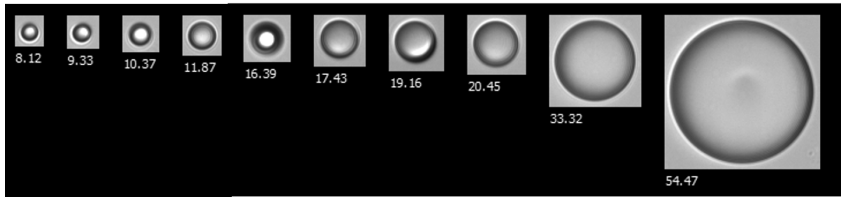


Apidra Pen Stressed (Agitation) 300 rpm 3 hrs.



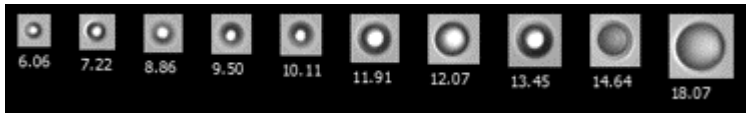
Representative Images from FlowCam LO: (A) Humalog and (B) Admelog

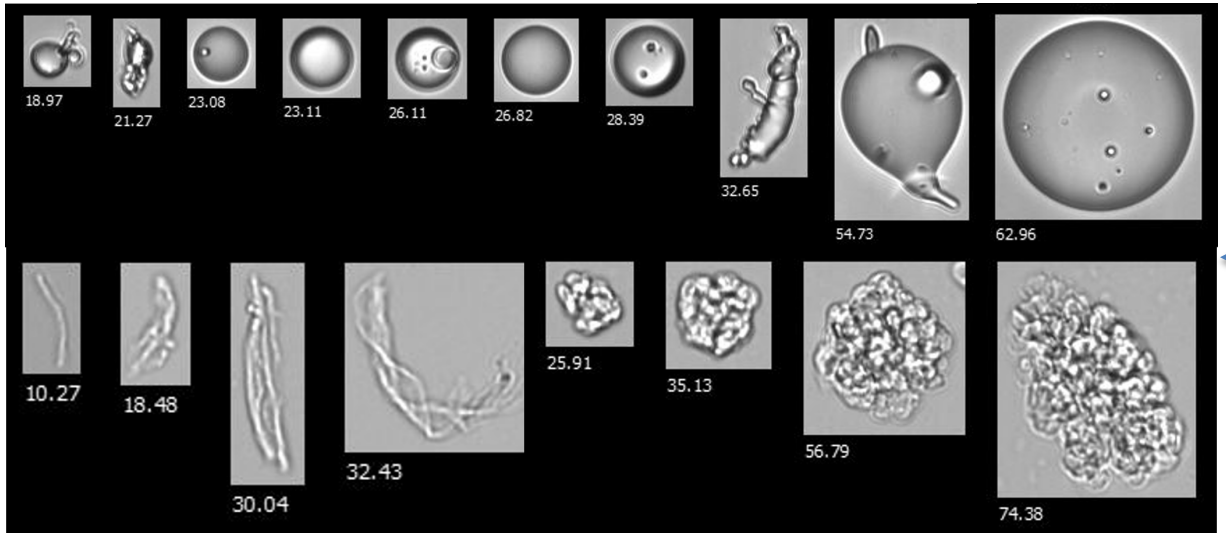
A)



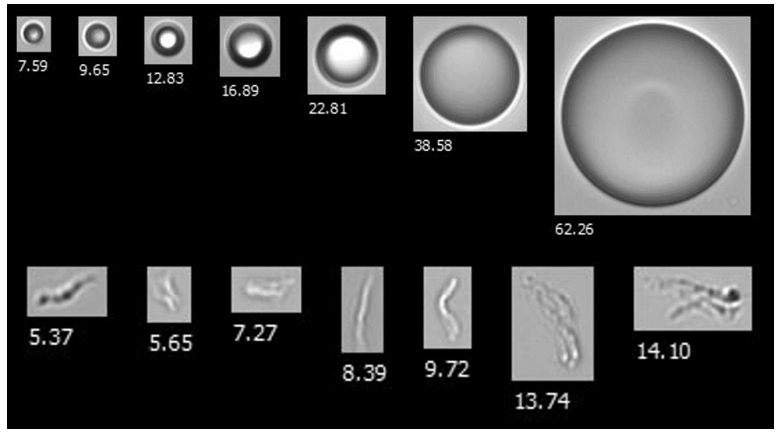
3 Day

B)



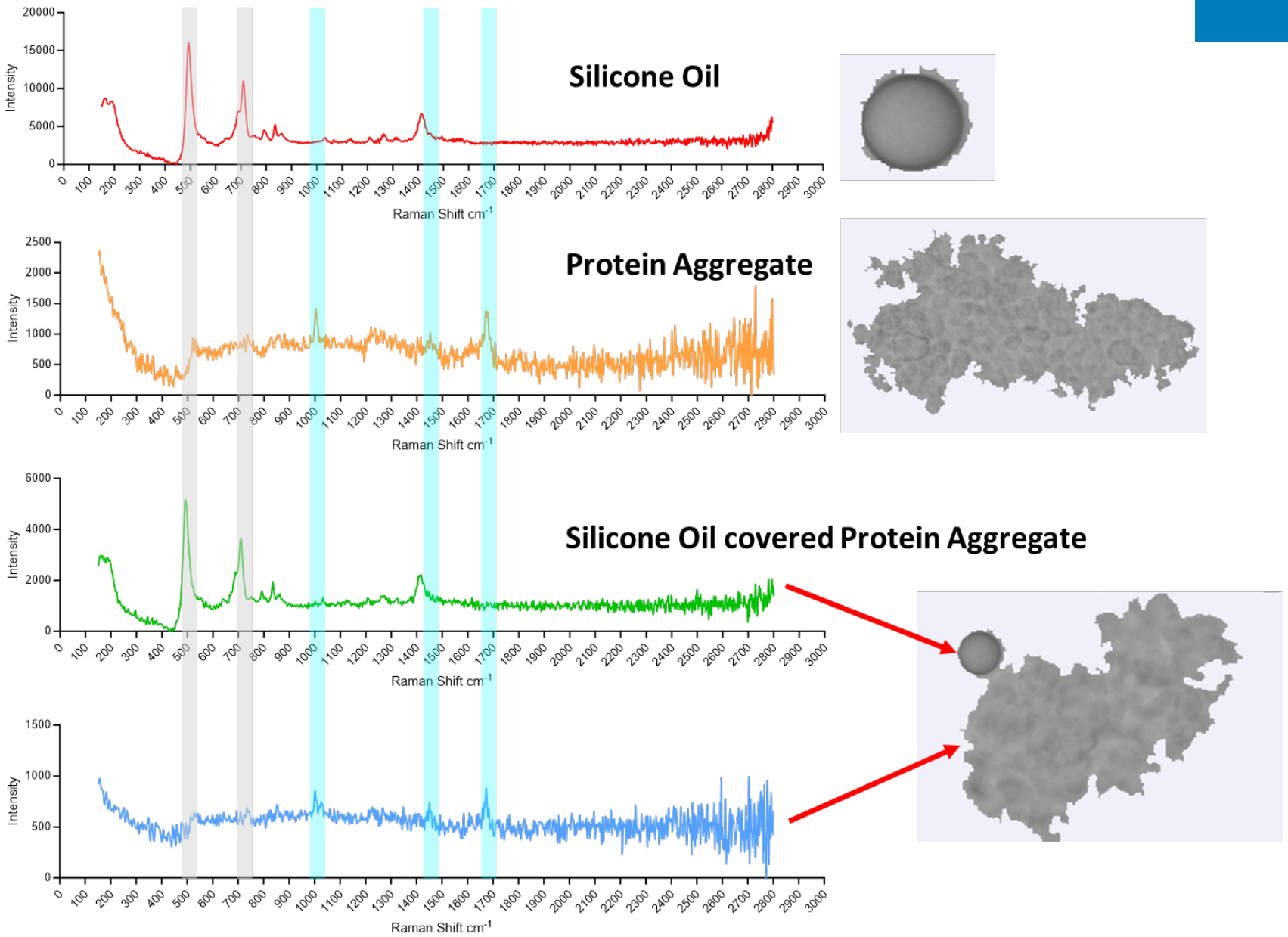


1 Week



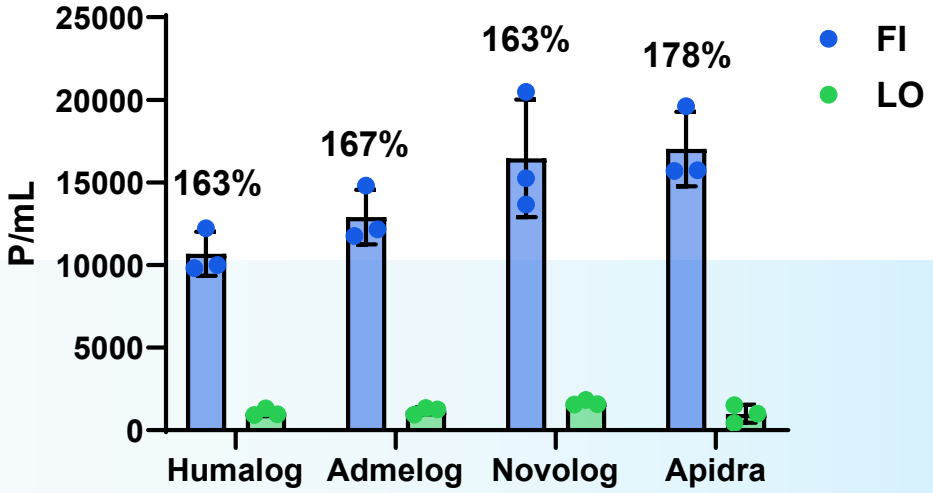
Suitability of the ETFE Particle as a Reference Standard Material: Morphological Data Histograms

Particle Chemical Identification with MDRS from Stressed Humalog Sample

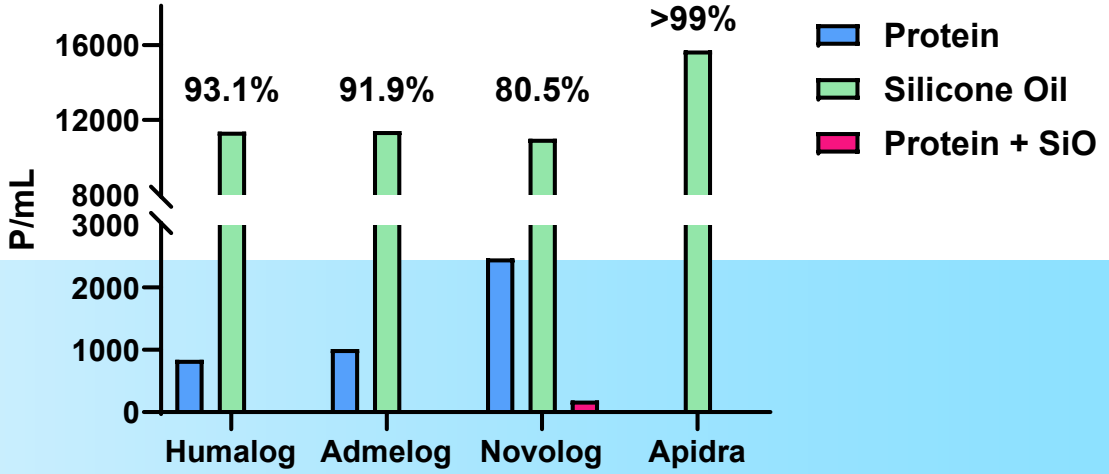


(A) FI vs LO and (B) Particulate Classification using AI

A)



B)



FI = Flow Imaging
LO = Light Obscuration

- **Control (unstressed) insulin drug products characterized using FlowCam LO and AI**

Acknowledgments

FDA

- Isabella de Luna (ORISE)
- Drug Product Quality Research Team Members

Collaborators

- OPQR
- OPQAIII
- NIST
- CDRH

Funding sources:

❖Oak Ridge Institute for Science and Education

❖ Manufacturing Science & Innovation Center of Excellence

❖Regulatory Science & Review Enhancement Program (CDER)

❖Critical Path (CDER)


FDA
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ADMINISTRATION

TOXICOLOGY OF SILICONES

Monica Pombo, PhD
USP/IQ Consortium Roundtable
07-Oct-2024

TOXICOLOGY OF SILICONES SCOPE

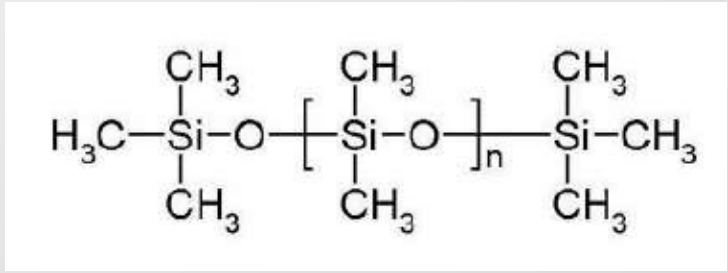
- Focused on an overview of Systemic Toxicity of Siloxanes
  - Parenteral Route of Administration: IV, IM, SC.

Table of Contents

SILICONE TOXICOLOGY
PDMS CHEMISTRY

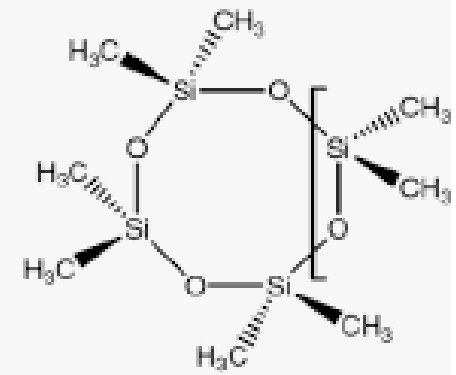
Linear polysiloxanes/ polydimethylsiloxanes (PDMS):

▸Polymeric organosilicon substances that are non-volatile (odourless), fluid (viscous) and virtually insoluble in water. They are commonly referred to as “silicones”.



SILICONE TOXICOLOGY
CYCLIC SILOXANES CHEMISTRY

Cyclic dimethyl polysiloxane compounds, Cyclomethicone is a generic name for several cyclic dimethyl polysiloxanes:
-cyclotrisiloxane (D3)
-octamethylcyclotetrasiloxane (D4)
-cyclopentasiloxane (D5)
-cyclohexasiloxane (D6)
-cycloheptasiloxane (D7)



D4 (representative structure)

SILICONE TOXICOLOGY
HUMAN EXPOSURE FOOD

- Dietary limits (by food category) range of 10 mg/kg (vegetables, other types of food and foodstuffs like oils and fats) to 100 mg/kg in chewing gum and 110 mg/kg in fruit-based desserts (Codex Standard 192-1995 (United Nations Food and Agriculture Organization and the World Health Organization[1]

- Antifoaming food additive E900 in the EU max level of 10mg/kg (solid food); 10mg/l in liquids[2]

- PDMS of viscosity 300 to 1,050 centistokes (cSt) is allowed by the US FDA as a defoaming agent up to 10 ppm (10 mg/l) in food. PDMS is also accepted by US FDA for use as a defoaming agent in the manufacture of paper and paperboard for packaging, transporting and holding of food products[3]

[1]Codex Alimentarius Commission, 2010
[2]CHPC, "Consumer Health Protection Committee, Committee of Experts on Materials Coming into Contact with Food. 2009
[3] US FDA 21CFR173.340

SILICONE TOXICOLOGY
HUMAN EXPOSURE

- Silicone Injection Therapy (intradermal/subcutaneous) with volumes ranging from 0.05 to 2ml[1]
- PDMS for treatment of flatulence –dose indication: 500mg/day (oral)[2]
- Human systemic exposure doses to D4 plus D5 exposure to cosmetic products (excluding oral products) 0.1 mg/kg bw per day based on a 60-kg individual[3]
- Silicone Implants: low molecular weight siloxanes plasma concentrations 79-92ng/ml of blood[4]
- PDMS lubricant is used in syringes, and amounts ranging between 150-250 mcg of silicone droplets or 30-40 mcg (insulin syringe or intravitreal applications)-> up to 30 mg in a year[5]

[1]Balkin SW, Dermatol Surg , 2005; Milojevic B, Aesth Plast Surg, 1982., Narins RS, Beer K. , Plast Reconstr Surg, 2006.
[2] Bibra Report 1991; Martindale 1989; Ingold CJ, Akhondi H. Simethicone. [Updated 2023 Jul 3]
[3] EC Scientific Committee on Consumer (SCCS) D4, D5, 2010.
[4] Flassbeck D. Anal. Chem. 2011
[5] Collier,Dawson, The Lancet 1985; 5. Chantelau, E., et al., 1986; Melo et al. 2009

SILICONE TOXICOLOGY REGULATORY LIMITS

- ADI of 850 mg/day, 17 mg/kg/day (50 kg human) (EFSA Panel on Food Additives and Flavourings (FAF))
- Oral ADI of 1.5mg/kg/day (FAO/WHO Expert Commission on Food Additives)
- FDA inactive ingredients database 240mg/day (oral) for dimethicone/simethicone

SILICONE TOXICOLOGY
PDMS PRE-CLINICAL SAFETY

- PDMS has low bioavailability
- Acute Toxicity:
  - Oral LD50 value range from >16 to >50 g/kg as tested in rats, guinea pigs and rabbits
  - After intravenous administration of PDMS, death has been observed as a consequence of PDMS causing pulmonary embolism[1] (physical attribute).
- Subchronic Toxicity:
  - No Observable Adverse Effect Levels for PDMS (NOAEL) > 1,000 mg/kg/day (oral, IV, SC / acute, sub-acute, sub chronic).
- PDMS is not a skin irritant and mildly to non-irritating to the eyes.
- PDMS is non-sensitizing to human skin.
- PDMS is not considered to have genotoxic or mutagenic activity.
- PDMS studies do not show any teratogenic or developmental effects (studies with rats and rabbits)

[1]ECETOC JACC, " (Second Edition), 2011; Price et al. American Journal of Forensic Medicine and Pathology, 2006.
BIBRA 1991, Joint FAO/WHO, Tech Report 2011,

SILICONE TOXICOLOGY
CYCLIC SILOXANES PRE-CLINICAL SAFETY

- Cyclic Siloxanes have low absorption/low bioavailability
- Acute Toxicity:
  - Oral LD50 value range from >2 to >4.8 g/kg as tested in rats
- Subchronic Toxicity:
  - Most relevant NOAELs for D4, D5, D6 range between 221 mg/kg/day to 1000 mg/kg/day (inhalation, oral, IV, SC).
- D4, D5, D6 are not skin irritants and are non-irritating to the eyes.
- D4, D5, D6 are non-sensitizing to human skin.
- Cyclic Siloxanes are not considered to have genotoxic or mutagenic activity.
- Some of the monocyclic siloxanes, especially D4 and D5, have been associated with reprotoxic and (thresholded, non-genotoxic) carcinogenic effects.

ECETOC JACC, " (Second Edition), 2011; BIBRA 1991, Joint FAO/WHO, Thech Report 2011,

SILICONE TOXICOLOGY SAFETY ASSESSMENT

- Silicone (as PDMS or cyclic siloxanes) can present during process development as impurities, extractables, and/or leachables from final products or manufacturing equipment

- **Safety assessment of Silicones (PDMS or Cyclic Siloxanes) <u>Pharamceutical Products</u>**

  - Following ICH Q3C guidelines*, a Permissible Daily Exposure (PDE) is calculated based on the available non-clinical data for each chemical.

  - Modifying factors to derive these permissible levels include species extrapolation, individual variability, study findings and duration, extent of observed effects, chemical characteristics.

*International Council For Harmonisation Of Technical Requirements For Pharmaceuticals For Human Use Ich Harmonised Guideline Impurities: Guideline For Residual Solvents Q3c(r8)

SILICONE TOXICOLOGY SAFETY ASSESSMENT

- Silicone (as PDMS or cyclic siloxanes) can present during process development as impurities, extractables, and/or leachables from final products or manufacturing equipment

- **Safety assessment of Silicones (PDMS or Cyclic Siloxanes) <u>Medical Devices</u>**

  - Following ISO 10993 guidelines (part 17), Tolerable Intakes are calculated estimating toxicological risk over time, i.e. different TI values for acute, subacute, sub-chronic and chronic exposures (which may utilize different PODs).

  - Uncertainty factors to derive these tolerable intakes include intraspecies variation, interspecies differences, quality and relevance of the experimental data, route to route extrapolations (ISO 10993 part 17)*.

*ISO 10993-17:2023Biological evaluation of medical devicesPart 17: Toxicological risk assessment of medical device constituents

SILICONE TOXICOLOGY

- Toxicity of Siloxanes/Silicone Particles
  - This presentation was focused on Systemic Toxicity (Parenteral Route of Administration: IV, IM, SC)

Other Toxicities

Silicone – Immunogenicity potential role as an adjuvant

Silicone- physical effects. i.e. droplets or large aggregates

ACKNOWLEDGMENTS

- Richard Hutchinson
- Michael Campbell, Sherry Parker
- IQ consortium/USP organizing committee for this opportunity

Disclaimer:

- **The opinions presented here are personal and do not represent the opinions of Johnson and Johnson Innovative Medicine.**

Thank you!

Challenges with Subvisible Particulates for Pre-Filled Syringe Products

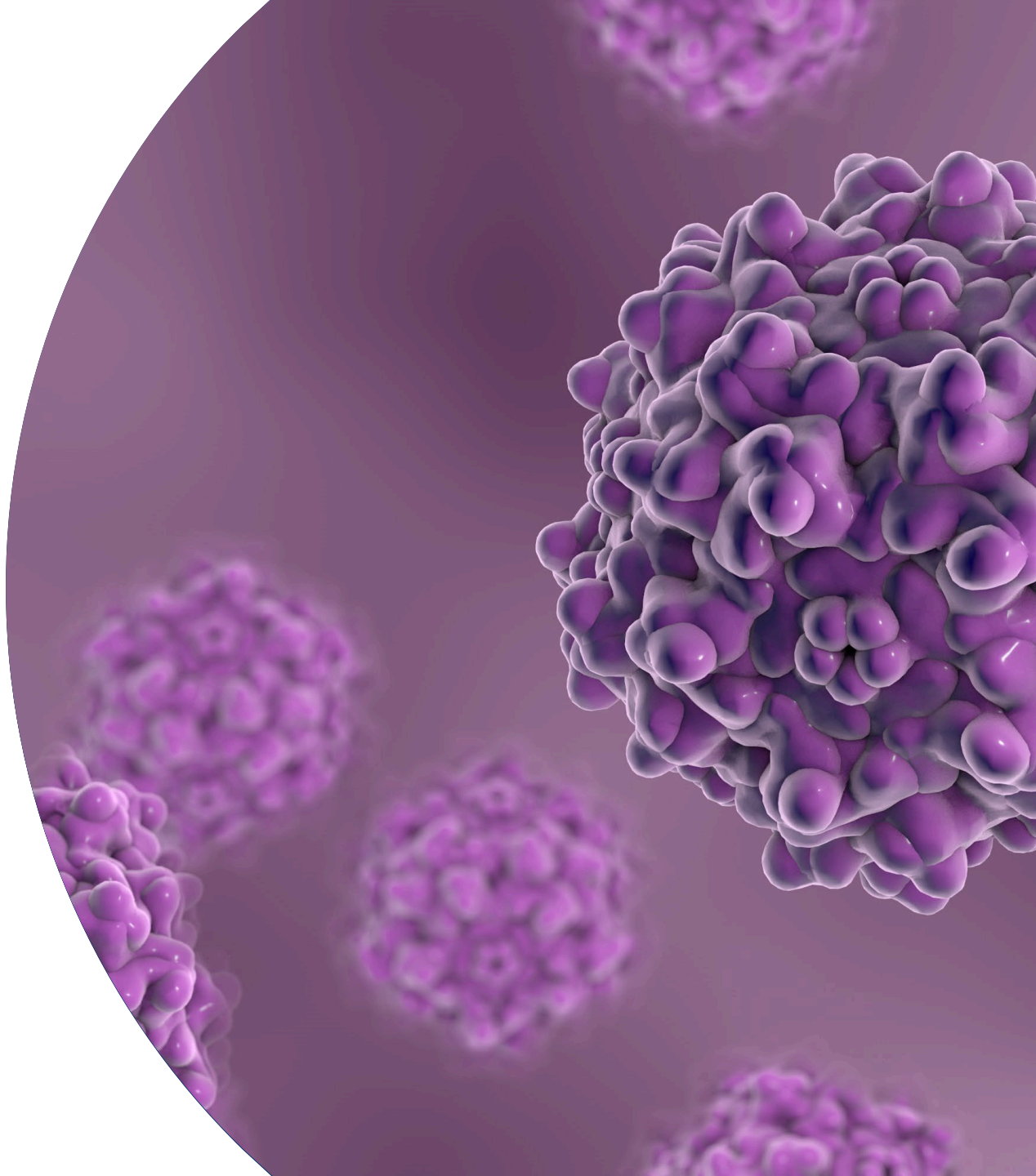
Bin Zhang, Shalini Minocha, Vinay Radhakrishnan

Injectable Drug Product Development

Alexion Pharmaceuticals Inc., AstraZeneca Rare Disease Unit

100 College St, New Haven, CT

07 Oct 2024



Outline

PFS Products and Silicone Oil

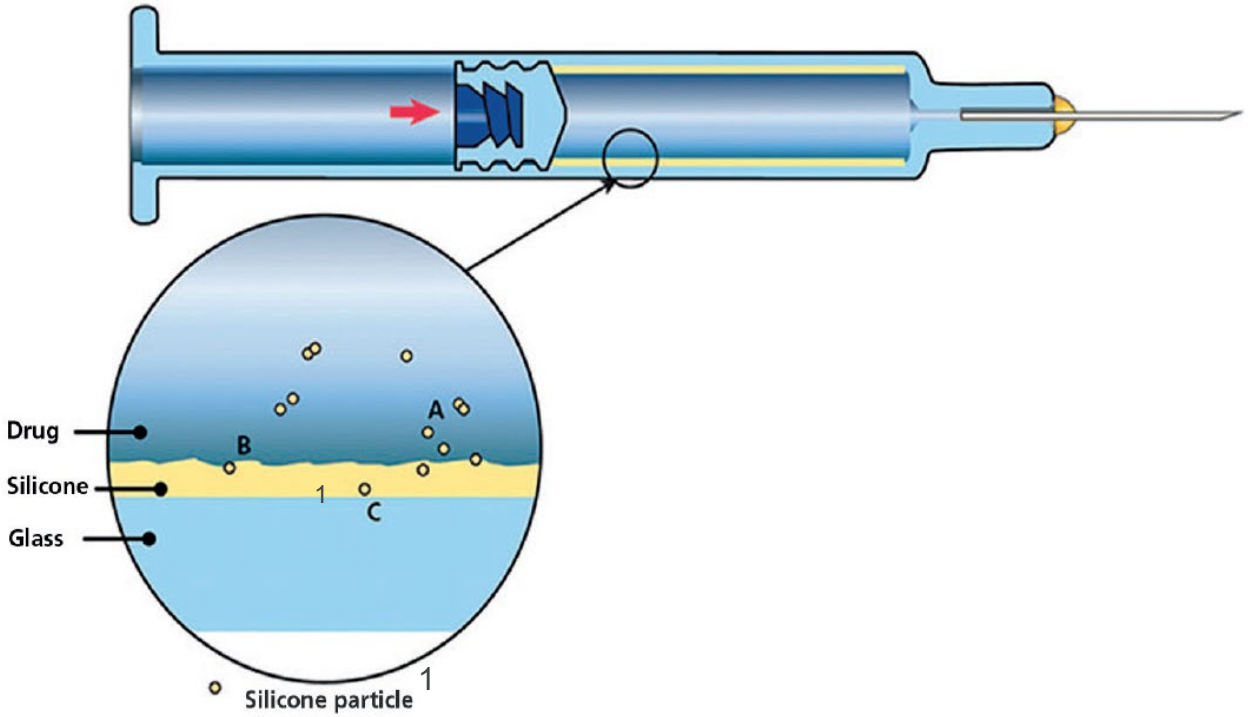
- Introduction of PFS with sprayed on silicone oil coating
- Challenges with silicone oil leaching
- Syringe siliconization Techniques

Analytical Techniques & Challenges in Assessing SVP in PFS Products

- Common quantification methods
- Characterization of SVP
- Regulatory guidance

Factors Influencing SVP in PFS products

- Root cause analysis with fishbone diagram



Pre-filled syringes (PFS) is preferred for at-home use/self administration

- Silicone oil layer coated on inner surface of syringe barrel to reduce resistance of plunger stopper against the inner syringe barrel
- Maintain low gliding force during storage of syringes – plunger moves smoothly with minimal resistance
- Stoppers and needles may also be siliconized

[1]Herget C, "An Innovative Solution to Address Silicone-Related Concerns". ONdrugDeliveryMagazine, Issue 64 (Feb 2016), pp 20-23

CHALLENGES WITH SILICONE OIL

- Silicone oil leached into drug products during transportation, storage and administration[1]

- Increased SVP counts during release and stability testing
  - ❑ Silicone oil droplets
  - ❑ Silicone oil induced proteinaceous aggregation[2]

- Potential for increased immunogenicity (no increased risk in In vivo and In vitro model[3])

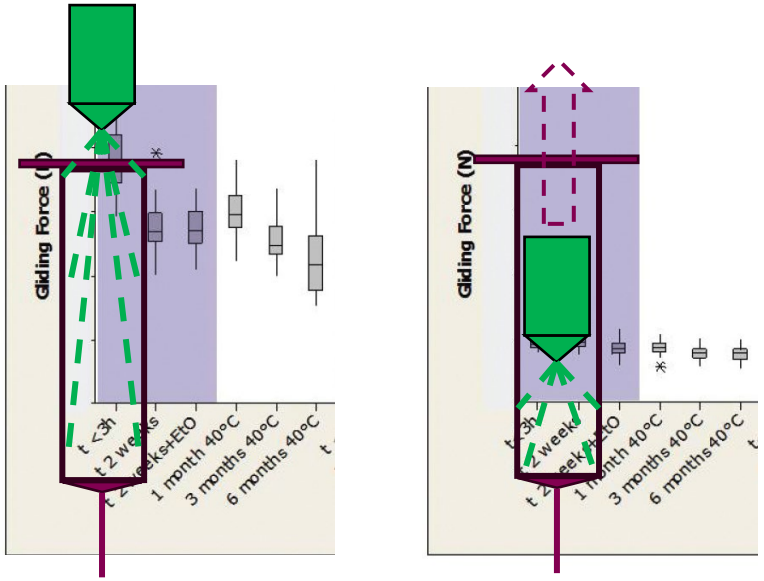
- Additional toxicological risk assessment may be required with leached silicone oil

[1]Gentile, K. et al. J. Pharm. Sci. 2023, 112, 2203-2211
[2]Jones, L. S. et al. J. Pharm. Sci. 2005, 94, 4. 918-927
[3]Joh, N. H. et al., J. Pharm. Sci. 2020, 109, 845-853

Spray On

Fixed Nozzle (e.g. BD Hypak)

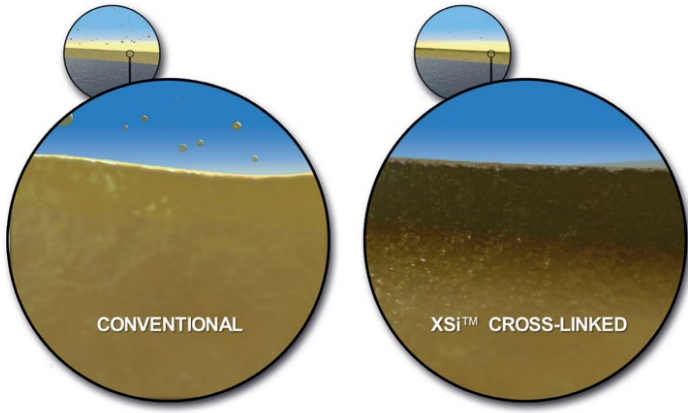
Diving Nozzle (e.g. BD Neopak)



- Diving nozzle provides optimized gliding force consistently at all silicone oil quantities[1]
- Different spay pattern of silicone oil leads to difference in coating uniformity

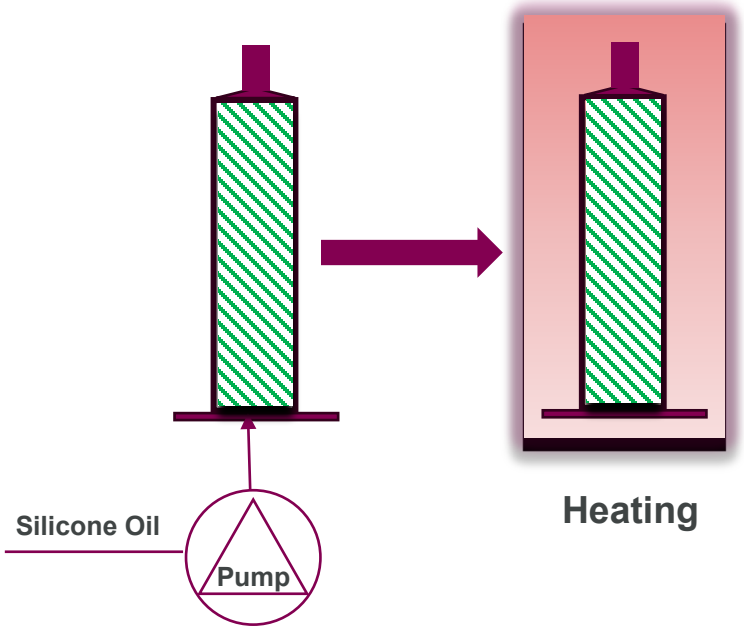
Silicone oil: 0.2-1 mg/syringe

Cross-Linked



- Cross-linked silicone chain networking leads to improved integrity of the lubricant layer[2]

Baked On



- Thermal fixate SiO emulsion by heating
- Lower BLGF compared to spray on
- Not suitable for staked needle

Silicone oil: <0.1 mg/syringe

[1]Wright, J. M. "PREFILLABLE SYRINGE TECHNOLOGY - BD Neopak - Delivering the Next Generation in Glass Prefillable Syringes". Drug Delivery, Featured Articles, Injection Devices. Issue:January/February 2014

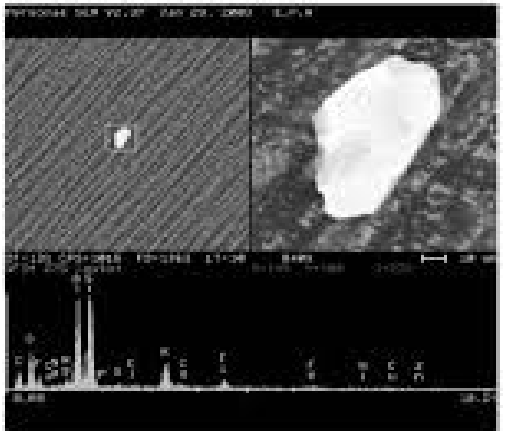
[2]Herget C, "An Innovative Solution to Address Silicone-Related Concerns". ONdrugDeliveryMagazine, Issue 64 (Feb 2016), pp 20-23

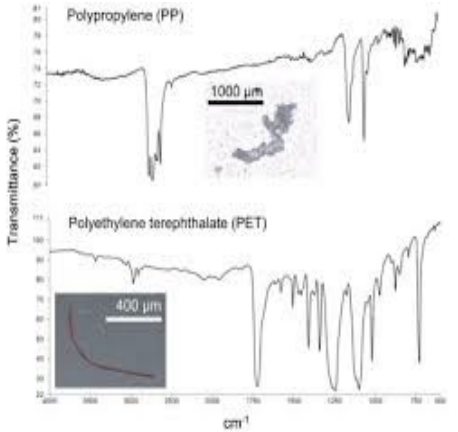
COMPARISON OF SVP QUANTIFICATION TECHNIQUES

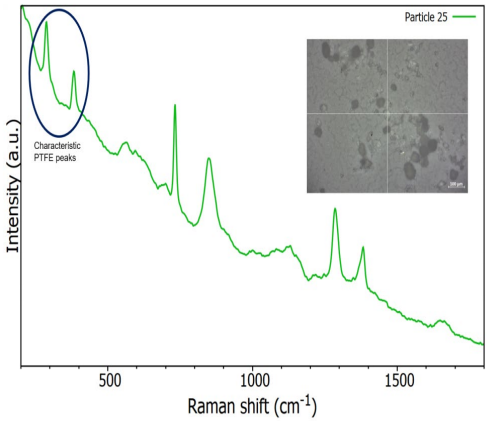
	Regulatory Guidance	Count/Size	Morphology	Particle Isolation	High Sensitivity	High Throughput
 Light Obscuration	Compendial ✓	✓	✗	✗	✓	✗
 Microscopic Particle Counting	Compendial ✓	✓	✓	✓	✗	✗
 Flow Imaging	Informational ?	✓	✓	✗	✓	✓

*Other quantification techniques (e..g. RMM, NTA) track lower size range < l-5 um

COMPARISON OF SVP CHARACTERIZATION TECHNIQUES







	SEM-EDS[1]	FTIR Microscopy[2]	Raman Microscopy[3]
Capability	• Particle EM image (isolated) • Elemental analysis	• Particle microscope image (isolated) • Molecular fingerprint	• Particle microscope image (isolated &suspended in liquid) • Molecular fingerprint
Sensitivity	• Electrically conductive Sample • Nanometer size	• Change in dipole moment • ~20 µm	• Change in polarizability • 5-10 µm
Challenges	• Particle isolation • Low-throughput	• Particle isolation • Background interference • Low-throughput	• Formulation components interfere (Fluorescence) • Low-throughput

[1]Beckman Coulter White Paper, Changes to USP <1788> Subvisible Particulate Matter
[2]Stockin, K. A. et al. Mar. Pollut. Bull. 2021, 173, 113084.
[3]https://www.edinst.com/identification-of-microplastics-using-raman-spectroscopy/

Compendial USP <787> & <788>

- Defines subvisible particle levels in injectable products
- No defined analytical strategy for silicone oil droplets
- Product specific specification with orthogonal technique is applicable

Informational USP <1787> & <1788>

- Silicone oil classified as intrinsic particles
- Silicone oil monitor and control on particle counts is critical to the overall particle control strategy
- Need to evaluate the impact of silicone oil on product stability
- Specifications with orthogonal technique should be set by the stakeholder and should be product specific, based on prior knowledge and risk assessment

FACTORS INFLUENCING SVP COUNTS

Fishbone Diagram

People

Machine

Analytical Methods

Material

Process

Mother Nature

SVPs in PFS Products

SUMMARY

- Silicone oil leaching from PFS leads to higher SVP levels in drug product in PFS vs vials
- Orthogonal methods and particle identification provide valuable information to monitor silicone oil particles in PFS DP
- Understanding of component, manufacturing process and incoming control prior DP manufacturing needed to ensure appropriate product quality control
- Nature of SVP in DP (Protein vs Silicone oil), factors that influence silicone oil leaching and impact of silicone oil on drug product quality are critical factors for DP quality

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AstraZeneca

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Thank You