INTERNATIONAL CONSORTIUM *for*
INNOVATION & QUALITY
in PHARMACEUTICAL DEVELOPMENT

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

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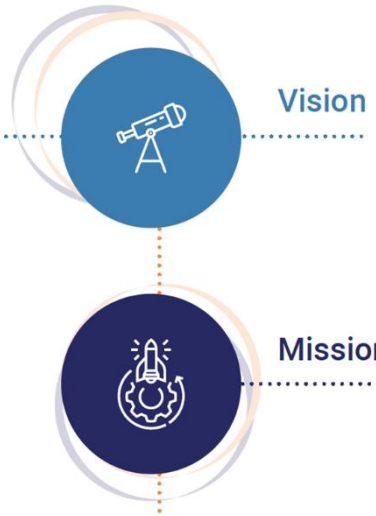
INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

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.

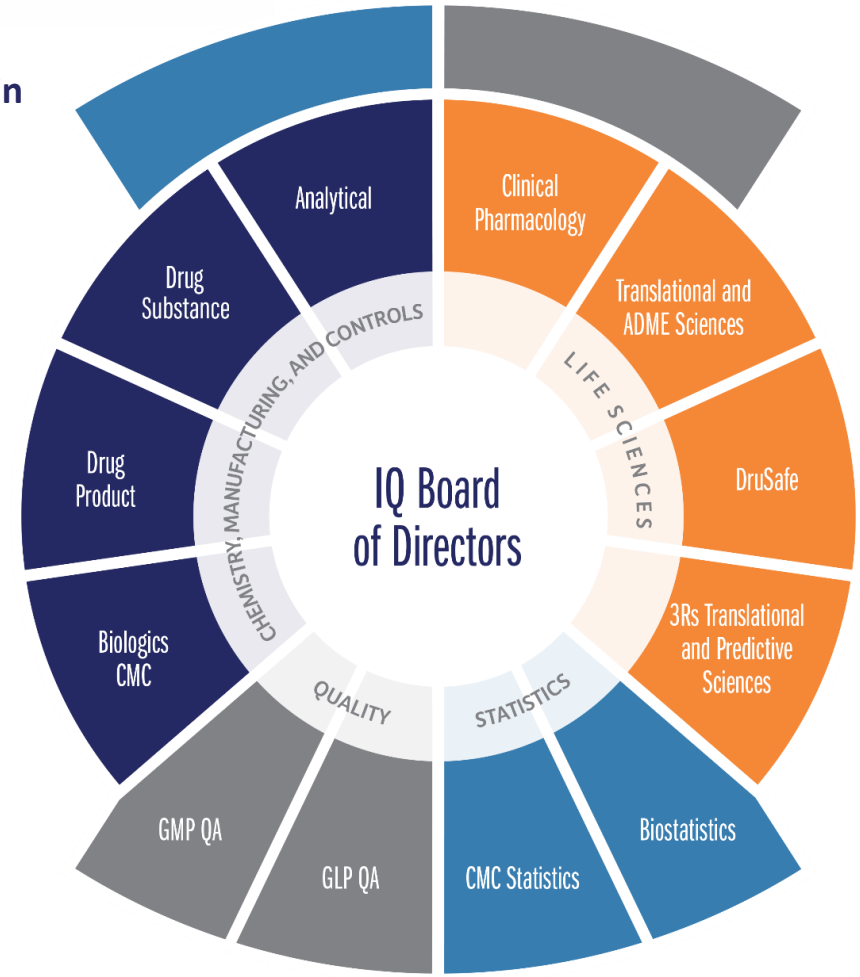


Vision

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

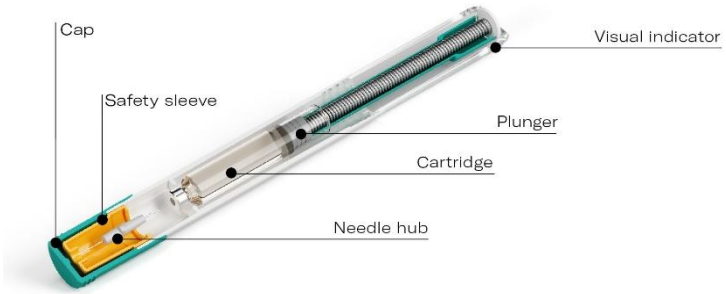
Mission

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 and form silicone oil droplets

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

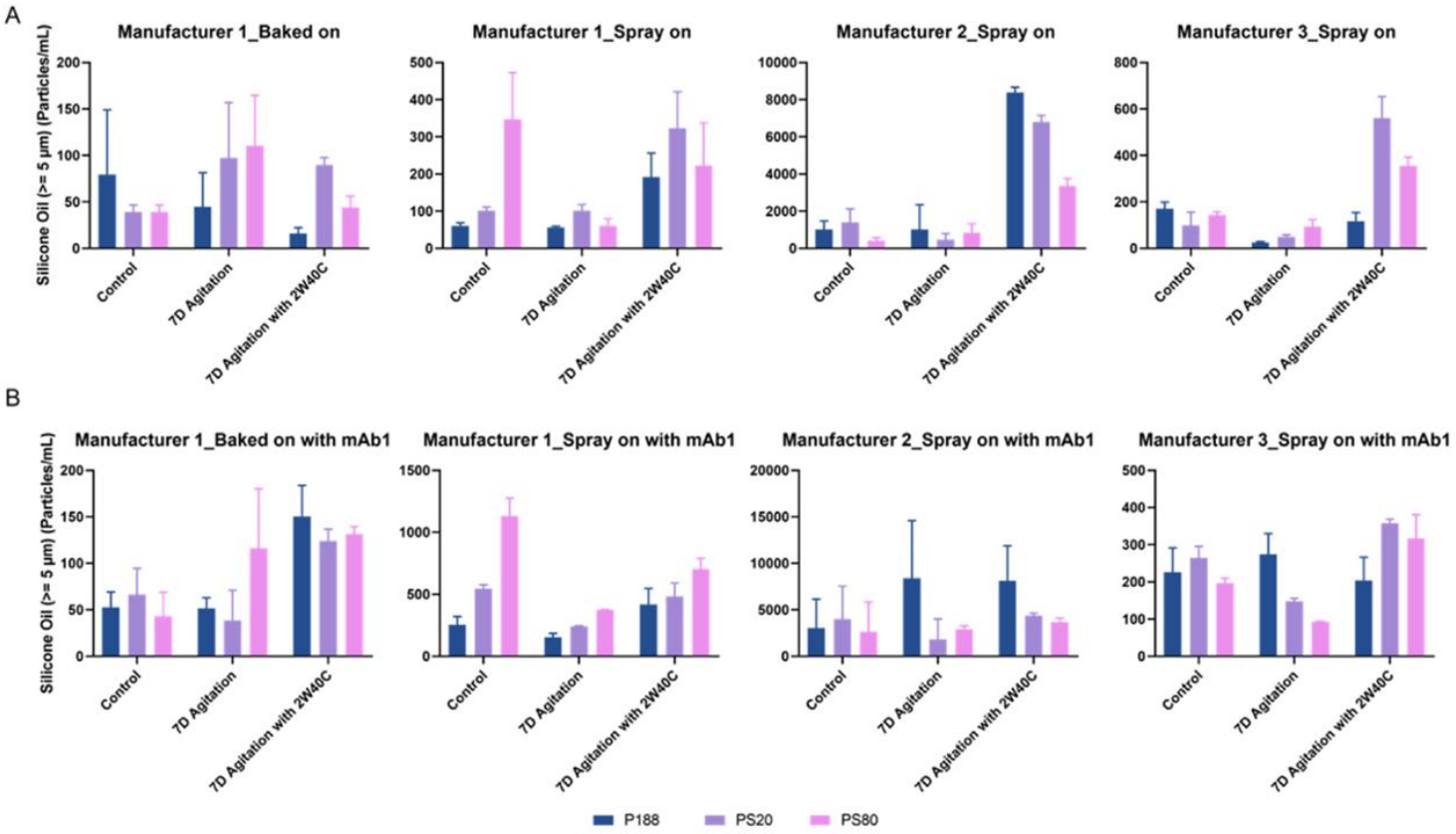


Fig. 4. MFI results of silicone oil ($\geq 5\mu$m) particle counts in the absence of protein (A) and presence of protein (B) with 0.02% (w/v) P188, PS20 and PS80, respectively, under control, mechanical stress, and combination stresses.

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

Silicone oil Can Act As Adjuvant At Very High Concentrations

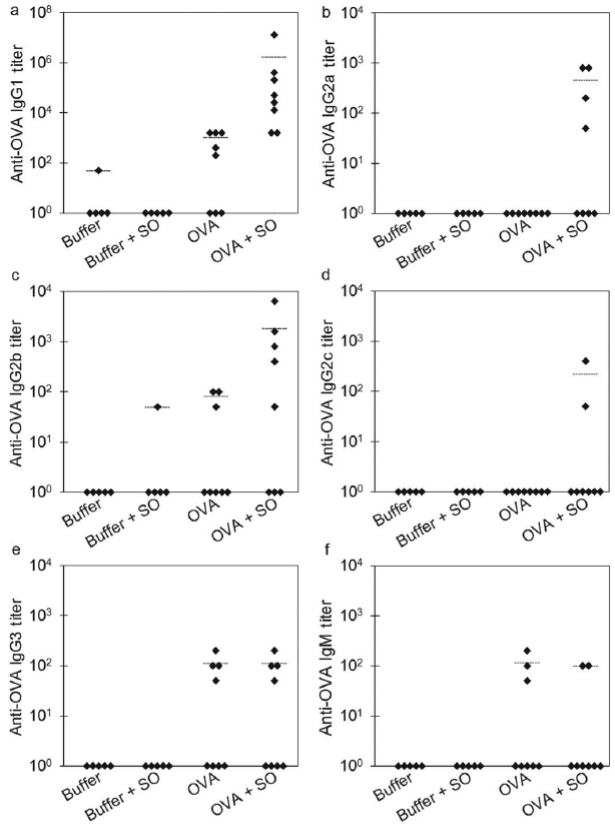
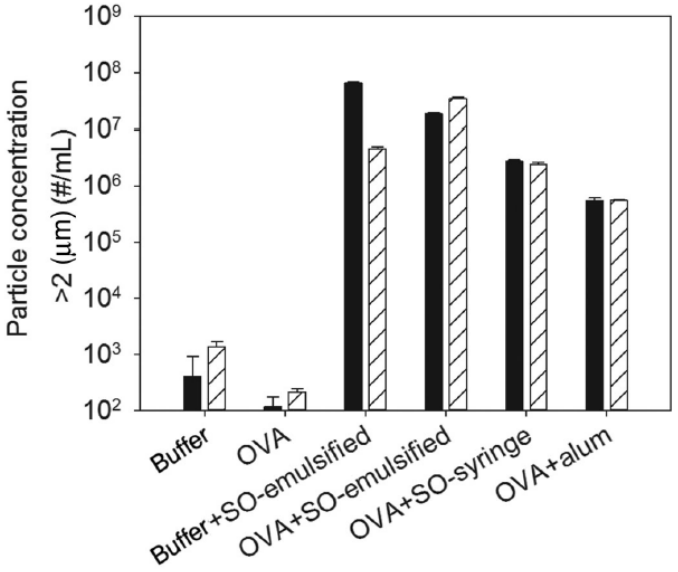


Figure 4. Anti-OVA antibody titers for mice treated with formulations of buffer, buffer that contained emulsified silicone oil microdroplets, OVA, and OVA that contained emulsified silicone oil microdroplets at day 29 for IgG1 isotype (a), IgG2a isotype (b), IgG2b isotype (c), IgG2c isotype (d), IgG3 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)

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Objective

“Evaluating Clinical Safety and Analytical Impact of Subvisible Silicone Droplets 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, bispecifics 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 polydimethylsiloxane (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

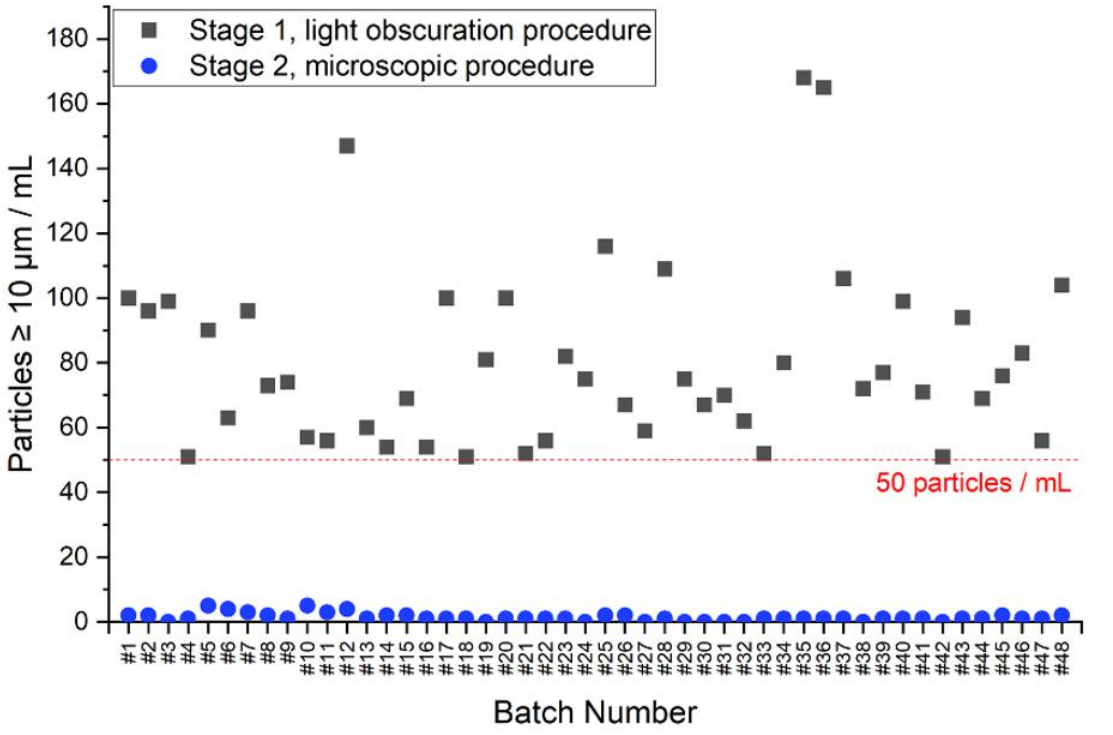
Also see slides from Monica Pombo (Toxicology J&J)
https://www.usp.org/events-training/subvisible-silicone-oil-droplets

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

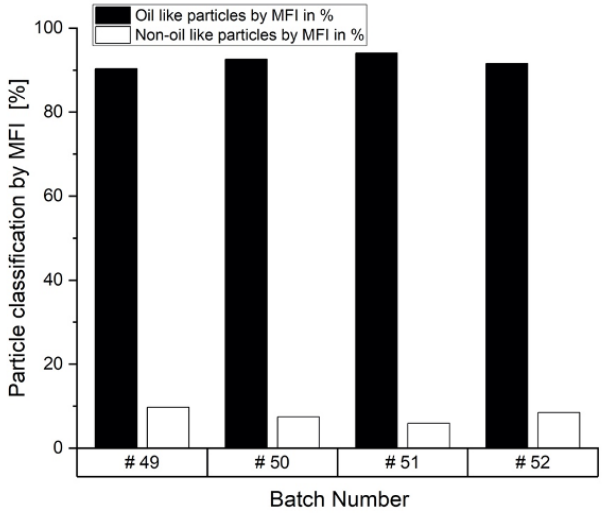
Case Study 1 - Batch Overview



- 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

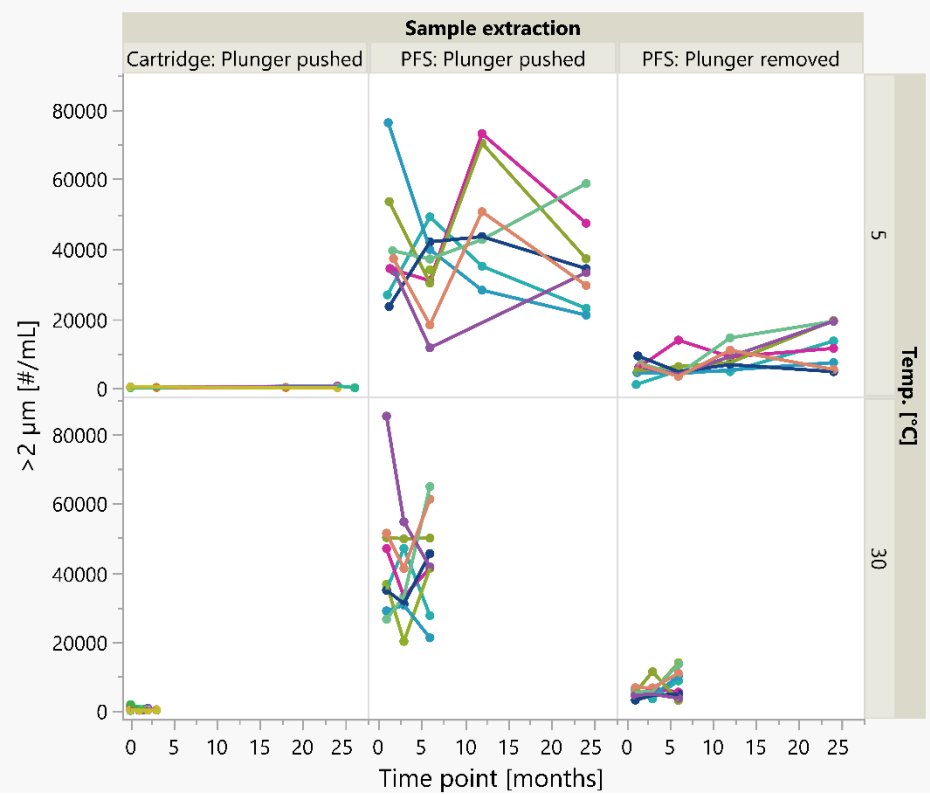
Batch	Particles ≥5 µm [/mL]	Particles ≥10 µm [/mL]	Particles ≥25 µm [/mL]	SiOP ≥5 µm [%]	Non- SiOP ≥5 µm [%]
#49	2109	127	2	90.3	9.7
#50	1312	72	5	92.6	7.4
#51	1801	96	2	94.0	6.0
#52	1944	91	11	91.5	8.5



- 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.

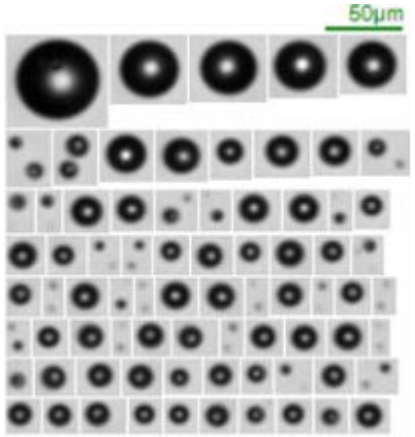
Case Study 2 - Compound B in Cartridge vs. PFS

- 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.
- 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
- When expelling the DP from a device, simulate the administration to the patient as good as possible. 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.
- There was no clinically meaningful impact on injection site reactions or immunogenicity of a DP with increased silicone oil droplets or content across a range of patient populations.
- Conflicting results on the effect of increased silicone oil droplets 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)

IQ/USP Roundtable

All the Particulars on Particles: Silicone Oil Droplets (On-Demand)

28-Sep-2023

https://www.usp.org/events-training/course/all-particulars-particles-silicone-oil-droplets-demand

USP/IQ Consortium Hybrid Roundtable on Subvisible Silicone Oil Droplets: Characterization Strategies, Impact on Product Development, and Clinical Safety

07-Oct-2024

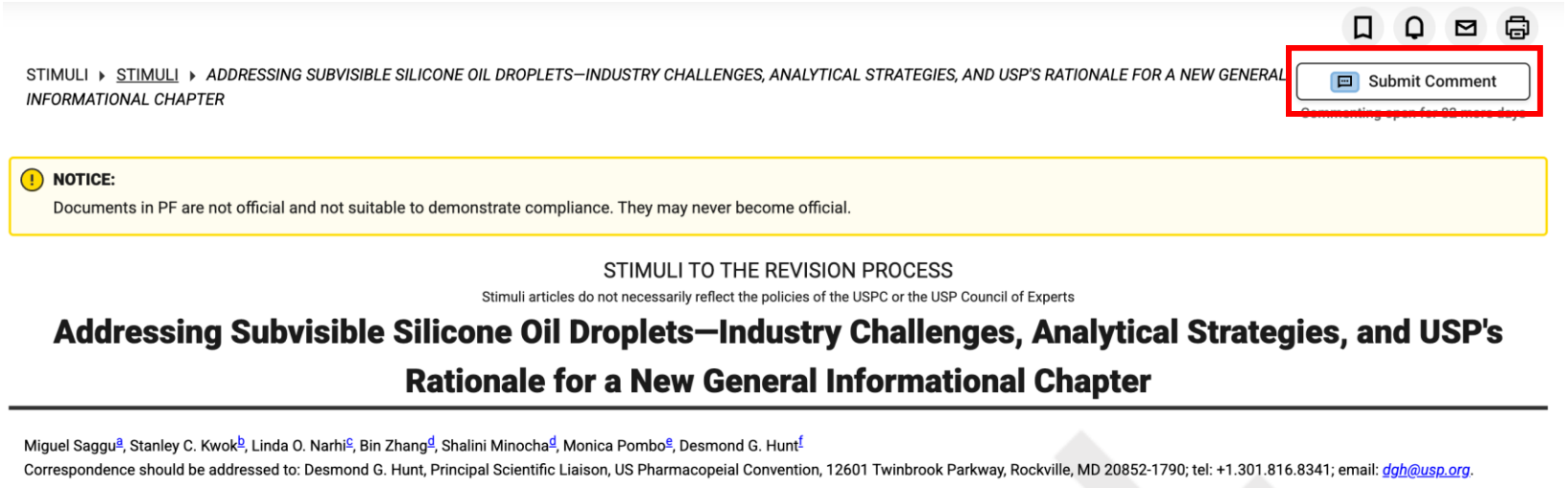
https://www.usp.org/events-training/subvisible-silicone-oil-droplets

- Round table discussion with Regulators, Industry and Pharmacopeia
    - USP drafts stimuli article and new informational USP guidance chapter

USP stimuli article

Posted in PF 51(6) – open for commenting until 31-Jan-2026

https://online.uspnf.com/uspnf/document/2_GUID-592AA9D6-F22A-4CAA-BED2-D23EFC8E1096_10101_en-US?source=emailLink&highlight=Silicone



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Addressing Subvisible Silicone Oil Droplets—Industry Challenges, Analytical Strategies, and USP's Rationale for a New General Informational Chapter

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