PARTICULATE MATTER FROM SYRINGES USED FOR INTRAVITREAL INJECTIONS

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Background: Syringes containing anti-vascular endothelial growth factor drugs to treat retinal diseases are prepared in different ways by various parties with syringe selection, preparation, and storage conditions affecting the risk of injecting particles into the vitreous. This study examines particle loads from various syringes over time.

Methods: Four syringes were studied: two plastic transfer syringes lubricated with silicone oil or oleamide, a glass syringe with baked-on silicone, and a lubricant-free polymer syringe. Syringes were rinsed with water or filled with buffer and analyzed over time; particles were quantified by flow imaging. Particle formation in a bevacizumab formulation was also characterized.

Results: Insulin syringes consistently showed very high particle counts. Oleamide-lubricated syringes had substantially fewer particles, but showed appreciable increases over time (leading to visible particles). Baked-on silicone glass syringes and lubricant-free polymer syringes both showed low particle levels ≥10 μm. Lubricant-free syringes showed the lowest particle levels ≥1 μm and the lowest particle levels with bevacizumab agitation.

Conclusion: Syringes have different intrinsic particle loads which can contribute to particle loads in the delivered drug. Oleamide-lubricated transfer syringes, commonly used for bevacizumab repackaging, have time-dependent particle loads and are associated with the formation of visible particles beyond 30 days of storage.

RETINA 41:827–833, 2021

Intravitreal injection of anti-vascular endothelial growth factor (VEGF) drugs to treat neovascular retinal diseases is one of the most commonly performed procedures in all of medicine.[1] In the future, pipeline drug developments are expected to improve anti-VEGF treatment durability and reduce injection frequency. However, given the aging population, the expanding indications for anti-VEGF therapy, and the recognition that chronic injection therapy may be required to maintain visual acuity gains over time,[2,3] the number of intravitreal injections is expected to continue to grow.

Also growing is an awareness around the potential for the presence of particles in intravitreal injections. Given the fact that the vitreous is a small, contained space and that neovascular retinal diseases typically require ongoing treatment, the risks associated with injecting particulate matter (including silicone oil) into the vitreous may be cumulative,[4,5] and particles may have association with complications such as floaters, sustained increase in intraocular pressure, and endophthalmitis.[6–9]

On-label injectable drug products are required, according to United States Pharmacopeia chapter <790>, to be "essentially free" of visible particles and USP <789> strictly limits subvisible particles in ophthalmic solutions. However, USP <789> is subject to interpretation. USP <789> was established before the practice of intravitreal injection of anti-VEGF drugs existed. It was originally intended for ointments, irrigants, and solutions but today, it is nonetheless the guiding document establishing limits for subvisible particles in intravitreal injections. The chapter references test methods outlined in USP <787> or USP <788> that require relatively large volumes of fluid for testing (pooling the contents of

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many syringes and optionally diluting), and as such, information on individual syringe performance is lost. According to USP <789>, the preferred test method is light obscuration, but membrane microscopy can be used if the product fails light obscuration testing. Although the light obscuration technique can count silicone oil and protein aggregates, membrane microscopy cannot see silicone oil droplets and may have difficulty counting protein aggregates. Furthermore, for drugs packaged in a vial and co-packaged with a transfer syringe for withdrawal and injection, there is no clear guidance in the chapter regarding what needs to be tested—the packaged drug or the delivered drug. Indeed, even if an anti-VEGF drug has low particle levels in a vial, if it is delivered by a transfer syringe, it may become contaminated by particulate matter from the syringe (including silicone oil) and the injected drug may not meet USP<789> limits. For off-label anti-VEGFs, it has long been known that repackaged bevacizumab contains high levels of particles (including silicone oil and protein aggregates).[5,10] Bevacizumab is indicated for IV infusion for oncology applications and, as such, must comply with the much less stringent particle requirements associated with USP <788>; thus, bevacizumab vials may not themselves meet USP<789> requirements.[11,12] Nevertheless, the high particle loads in repackaged bevacizumab are primarily tied to the use of siliconized transfer syringes for the repackaging.[10,13]

Over the past few years, the Food and Drug Administration (FDA) has taken steps to define[14] and enforce[15] particle-related regulations in the 503B outsourcing facility industry. Notably, the FDA guidance for repackaging biologics, issued in January 2018,[14] requires injections to be inspected for visible and subvisible particles and references USP chapter <789> for subvisible particle limits. The FDA draft guidance for current good manufacturing practices at 503B outsourcing facilities also recommends visible particle limits be established for all compounded drugs and cites USP <790>.[16]

Despite the existing regulations, there are less data on which syringes, transfer or storage systems will minimize the risk of particulate injection into the vitreous cavity. Syringes used to store and/or transfer anti-VEFG drugs for intravitreal injection are themselves contributors to overall particle loads. This contribution can be direct (intrinsic or extrinsic particles shedding from the syringe, silicone or other lubricants, rubber, cellulose etc.) or indirect (e.g., syringe particles or syringe surfaces interacting with the drug leading to protein aggregation). Proteins are designed by nature to be interactive with and responsive to their environment and are thereby subject to chemical and conformational changes. One protein molecule can simultaneously carry regions of hydrophobicity, hydrophilicity, and positive and negative electrostatic charge. As a result, proteins can adsorb at surfaces and interfaces and aggregate by heterogeneous nucleation at particle surfaces. If the adsorption/desorption process is irreversible, composite aggregates can form, or the drug may undergo a chemical or conformation change that can be a precursor to aggregate formation.[17] This may affect the potency or dose of the drug delivered, and introduce particulates into the eye.[18] The overall risk of the syringe directly or indirectly contributing to the particle loads in the injected drug will depend on many factors including foremost, the syringe selection (materials of construction, lubricants, manufacturing environment etc.), and the duration of contact with the drug, agitation, and the formulation composition.

Various types of transfer and prefilled syringes are used globally for intravitreal injections of anti-VEGF drugs. Table 1 outlines the syringe filling scenarios used to prepare the injections. It is important to recognize that different routes of injection preparation (point of care syringe filling/repackaged/prefilled) affect the syringe selection and storage time, and therefore the risks associated with injecting particulate matter.

This study investigates particle loads originating from various syringes themselves, in the absence of drug, by rinsing the syringes with particle-free water (to mimic short term contact relevant to filling Scenarios 1–3) or by filling the syringes with a placebo buffer solution and storing for up to 90 days (to mimic medium to longer-term contact relevant to Scenarios 3–5).

Materials and Methods

Syringes

The syringes used in this study are pictured in Figure 1A. Two plastic transfer syringes and two "prefilled" syringes were used in this study. (We here distinguish "prefilled" syringes from "transfer" syringes as containers intended for long-term storage, usually filled from the back end by drug manufacturers). The transfer syringes included were the 0.5-mL staked needle BD polypropylene siliconized insulin syringe (herein referenced as "siliconized plastic insulin transfer syringe") and the 1-mL Luer slip tip Henke-Sass Wolf NORM-JECT Tuberculin syringe ("oleamide-lubricated plastic transfer syringe"). Both are commonly used for bevacizumab repackaging and for withdrawal of an anti-VEGF drug from a vial and

Table 1. Ophthalmic Injections of Anti-VEGF Drugs May be Prepared in a Variety of Different Ways by Different Parties, Making Different Syringe Selections, With Varying Durations of Contact Between Drug and Syringe

	Syringe Filling Scenarios	Who Selects the Syringe?	Typical Syringe Used Today	Typical Drug Storage Time in Syringe
1	Physician fills syringe by withdrawal from vial at point-of-care using off the shelf syringe	Physician	Polypropylene or polycarbonate transfer syringe. Siliconized or lubricated with oleamide.	Minutes
	Physician fills syringe from kit (combination product: Vial + co-packaged syringe) at point of care			
2	Syringe filled by 503A pharmacies	Drug manufacturer 503A pharmacy		Minutes
	Syringe filled by 503B outsourcing facilities			
3				Hours to weeks
4		503B outsourcing facility		1–3 months
5	Drug originally packaged by manufacturer in prefilled syringe	Drug manufacturer	Glass with baked-on silicone	Up to 2 years

injection. The prefilled syringes used were a 1-mL Luer lock ("baked-on silicone glass syringe") with a NovaPure plunger and the 0.5-mL Luer lock Daikyo Crystal Zenith (CZ) cyclic olefin polymer syringe ("silicone-free, lubricant-free COP syringe").

Sample Preparation for Syringes Rinsed With Water

All syringes were filled in an uncontrolled laboratory environment. Approximately 0.5 mL of sterile filtered water for injection, was drawn into the syringes and immediately dispensed into the flow imaging instrument (0.2 mL is used to rinse the flow cell and 0.3 mL is used for the measurement). Our studies show that particle levels reported in #/mL are independent of fill volume (manuscript in preparation) and as such, these conditions are meant to mimic the clinical situation in which a drug is withdrawn from a vial and is subsequently injected into the eye.

Sample Preparation for Syringes Filled With Buffer and Aged

All syringes were filled in an ISO 5 cleanroom to minimize environmental contamination. Phosphate buffer (50 mmol/L sodium phosphate, 0.4 mg/mL polysorbate 20) was filtered through a 0.2 μm filter. The buffer as prepared contained small baseline particle counts (59.0 ± 13.0, 6.2 ± 1.6, and 0.6 ± 1.2 for size categories ≥ 10 μm, ≥ 25 μm and ≥ 50 μm, respectively) identified by micro-FTIR as polypropylene and natural rubber (likely originating from the container in which it was stored/prepared). Because of the inherent variability in flow imaging particle counting, these baseline buffer particle counts are not subtracted from the reported syringe particle counts. A volume of 0.5 mL of the buffer was drawn into the 0.5 mL BD insulin and 1 mL NORM-JECT syringes. A clean, silicone-free glass syringe with a needle was used to fill 0.5 mL of buffer into the 0.5-mL Daikyo
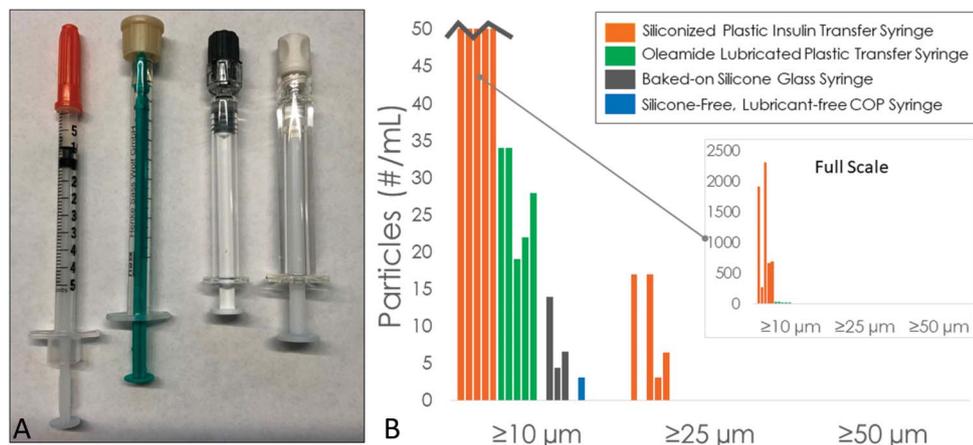

Fig. 1. A. Syringes used in this study. From left to right: BD siliconized plastic insulin transfer syringe, NORM-JECT oleamide-lubricated plastic transfer syringe, baked-on silicone glass syringe, Daikyo Crystal Zenith silicone-free, lubricant-free COP syringe. **B.** Particle levels from water rinsing of assembled syringes. Each bar represents a particle measurement from a single syringe without pooling. The inset graph shows the particle counts from the insulin syringe at full scale.

Crystal Zenith syringes and the 1-mL baked-on silicone glass syringes through the Luer tips. Assembled syringes were agitated along the main axes on a rocking table at 80 motions per minute for 1 hour. Syringes were then packed into individual pouches and placed into a carton with layers of gel packs and bubble wrap. The carton was then subjected to handling based on ASTM D4169—14.[19] Subsequently, syringes were stored, refrigerated at 2 to 8°C for 15, 30, 60, or 90 days. After storage, syringes were agitated for 1 hour before testing. Measurements were made in replicates of five syringes.

Sample Preparation for Syringes Filled With Bevacizumb

A 1 mg/mL bevacizumab solution was prepared by dilution of the 25 mg/mL stock with placebo buffer. Baked-on silicone glass syringes and silicone-free, lubricant-free COP syringes were filled to 0.5 mL as described above and rotated end over end at 10 RPM for 24 hours.

Microflow Imaging

Microflow imaging (FlowCam 8,000, Fluid Imaging Technologies, Inc. Scarborough, Maine) was used to record digital images, enumerate particles, and determine size distributions (≥ 1 μm). The entire 0.5-mL volume of each syringe was used without dilution, for flushing of the sample cell and particle measurement of the remaining 0.3-mL sample. It should be noted that the fluid imaging methodology is not currently included in USP <787>, <788>, or <789>. However, the strengths of this technique are its ability to measure particle counts in small sample volumes from single syringes without pooling and its ability to capture images of the particles that can provide indirect information regarding particle composition.

Results

Particle Levels With Water Rinsing

Figure 1B shows particle levels (1–100 μm) resulting from water rinsing of the different syringes. Using a siliconized plastic insulin transfer syringe to draw up and dispense a fluid, even without any protein content or storage time, results in high, and highly variable, particle levels from the syringe—nearly two orders of magnitude greater than USP<789> limits. Images captured by the FlowCam indicate that most particles detected are silicone oil droplets. Particle loads from the syringes with water rinsing rank as: siliconized plastic insulin transfer syringe > oleamide-lubricated plastic transfer syringe > baked-on silicone glass syringe > silicone-free, lubricant-free COP syringe.

Particle Levels With Buffer Storage

The images shown in Figure 2 are visual representations of the particle counts (1–100 μm) from each of the four syringes containing phosphate buffer, subjected to an industry-standard agitation/shipping simulation and stored refrigerated for 15 days. Each black pixel signifies a particle, regardless of size or morphology, and the x-y distribution corresponds to the particles' spatial distribution on the instrument detector as they pass through the flow cell. Most particles from the insulin syringe are silicone oil, as evidenced by the FlowCam images showing characteristic round black particles with white centers (not shown).

Particle counts after 90 days of storage are shown in Figure 3. In all size categories shown in Figure 3A, the siliconized plastic insulin transfer syringes had the greatest number of particles, followed by the oleamide-lubricated plastic transfer syringes. Within the three size categories referenced in USP <789>, the baked-on silicone glass syringe and the silicone-
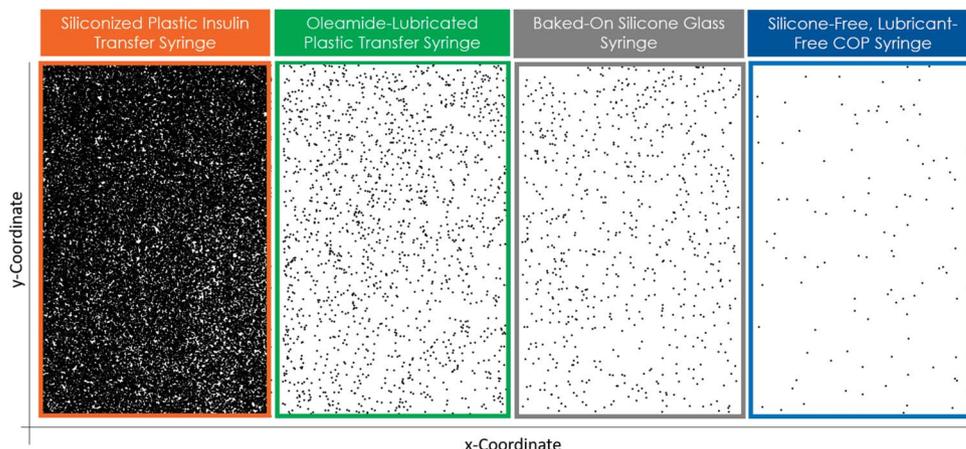

Fig. 2. Flow imaging particle counts (all particles >1 μm) as x-y spatial plots on the instrument detector. Syringes were filled with approximately 0.5 mL of buffer (no drug product), subjected to ASTM D4169 to 14 drop/shipping testing, and stored for 15 days at 2 to 8°C.
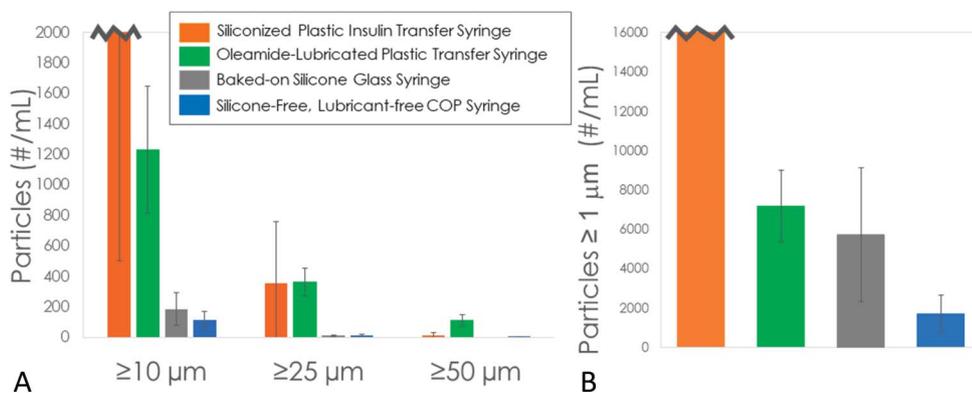
Fig. 3. Flow imaging particle counts from syringes filled with approximately 0.5 mL of buffer (no drug product), subjected to ASTM D4169 to 14 drop/shipping testing, and stored for 90 days at 2 to 8°C. **A.** shows cumulative counts in the size categories relevant to USP <789> and (**B**) shows all particles greater than 1 μm. Error bars represent SDs.

free, lubricant-free COP syringe appeared to perform similarly, with particle loads indistinguishable from the baseline buffer particle counts. When all particles greater than 1 μm are considered (Figure 3B), the baked-on silicone glass syringe shows higher particle counts than the silicone-free, lubricant-free COP syringe and less of an advantage over the oleamide-lubricated transfer syringe because of the high levels of particles in the 1 to 10 μm range from the baked-on silicone. FlowCam images indicate that most of these particles are silicone oil droplets.

Of the four syringes, only the oleamide-lubricated transfer syringe showed a notable time dependence in particles. Figure 4 shows the particle counts from each individual oleamide-lubricated transfer syringe measured at the four different time points. Although relatively low particle levels are noted at the 15- and 30-day timepoints, there is a substantial increase at the 60- and 90-day time points (roughly 4 to 6-fold increase between the 30 days and 60 days). Furthermore, visible particles were noted in two of the five oleamide-lubricated plastic transfer syringes at the 60- and 90-day time points. The images inset in Figure 4 show characteristic particles detected by after 90-day

aging. FTIR analysis of the inner surface of this transfer syringe confirmed the presence of an oleamide-type lubricant. Together with the amorphous FlowCam images, this suggests that the oleamide lubricant may be migrating off the inner barrel wall into solution over time and creating visible particles.

Effects of Agitation on Bevacizumab Aggregation

The baked-on silicone glass syringe appeared to have similar numbers of particles ≥10 μm compared with the silicone-free, lubricant-free COP syringe. However, baked-on silicone glass syringes showed particle loads in the 1- to 10-μm range that were approximately 3.5 times higher than the silicone-free, lubricant-free COP syringe. To understand the potential impact that these small silicone droplets may have on protein aggregation, particle formation with agitation of a 1 mg/mL bevacizumab solution was investigated. Whereas the syringe alone seems to have similar particle loads ≥10 μm, the baked-on silicone glass syringe resulted in more than twice the particle counts in the bevacizumab solutions compared with the silicone-free, lubricant-free COP syringe in the
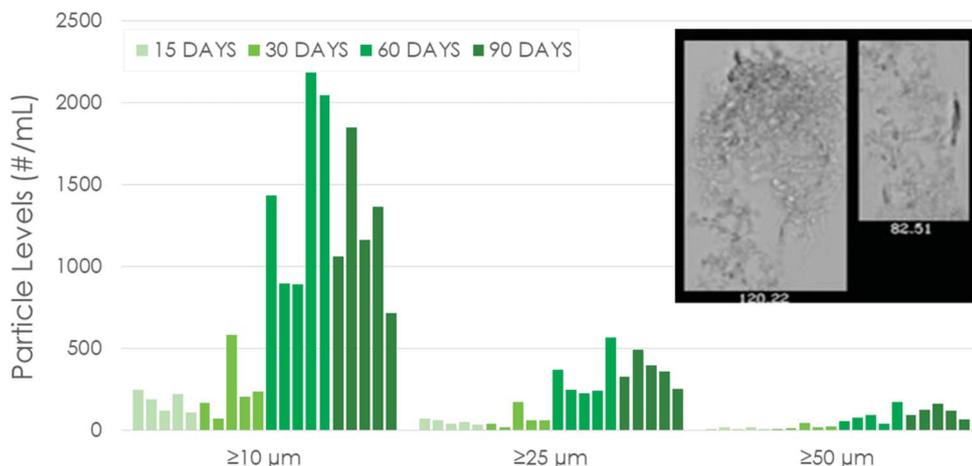

Fig. 4. Time evolution of particle counts in NORM-JECT silicone-free, lubricated plastic transfer syringes filled with buffer (no drug product). Each bar represents one single syringe and five syringes were measured at each time point: 15, 30, 60, and 90 days of storage. The inset image shows characteristic particles detected by FlowCam in the NORM-JECT syringes at 90 days.
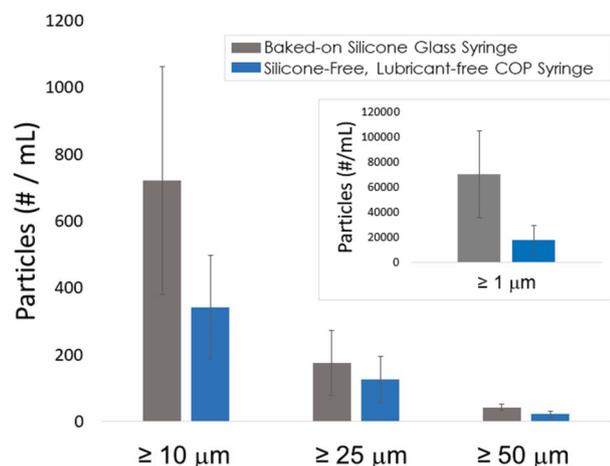
Fig. 5. Comparison of relative particle levels in 1 mg/mL bevacizumab solution after 24 hours agitation (end over end rotation at 10 RPM) in a baked-on silicone glass syringe (grey bars) versus a silicone-free, lubricant-free COP syringe. Error bars represent SDs.

≥ 10 μm range, and close to 4 times the particle counts in the ≥ 1 μm range as shown in Figure 5. FlowCam images showed high numbers of amorphous particles consistent with proteinaceous particles.

Discussion

Recently, there has been increasing scrutiny over the syringes used to repackage bevacizumab for intravitreal injection. In a study presented at the 2019 American Society of Retina Specialists Annual Meeting, it was found that between 14% and 78% of eyes injected with bevacizumab from different siliconized BD transfer syringes had silicone oil microdroplets in the vitreous.[20] The growing awareness of the high silicone loads from insulin syringes has led some, but not all, 503B outsourcing facilities to discontinue the use of this syringe.[21] Furthermore, in May of 2019, the FDA issued a 483 letter to a registered 503B outsourcing facility which was the first of its kind to include an observation pertaining to the continued use of siliconized BD hypodermic syringes for bevacizumab repackaging despite the syringe manufacturer's notification that intraocular use of the syringes has been associated with events such as floaters and endophthalmitis.[15] It should be noted that insulin syringes are also commonly used globally to withdraw drug product from a vial and inject it into the vitreous (Scenario 1 in Table 1). Our water rinsing studies (Figure 1) show that this practice results in the injection of silicone oil droplets—even when the drug is not stored in the syringe. We have measured an average of 1,179 particles/mL ≥ 10 μm originating from the insulin syringe with simple water rinsing. For reference, the USP $<789>$ limit is 50 particles/mL ≥ 10 μm.

NORM-JECT (oleamide-lubricated plastic transfer) syringes have recently become a preferred option for bevacizumab repackaging,[22] because of the above-mentioned concerns over the injection of silicone oil. Figures 2 and 3 show that these syringes have significantly lower particle loads compared with insulin syringes. However, although NORM-JECT syringes are silicone-oil-free, they are not lubricant free; the piston gliding is facilitated by an oleamide lubricant. Our studies show that over time, particle loads in NORM-JECT syringes increase significantly, possibly because of the migration of the lubricant into solution. Although the clinical consequences of the injection of amorphous oleamide particles into the vitreous are not understood, an important practical consequence of these particles is the potential for high reject rates of filled bevacizumab syringes—either by the outsourcing facility doing the repackaging (failure to pass vision inspection and/or USP $<789>$ subvisible particle testing) or by physicians observing visible floaters at the point of care. Furthermore, such lubricant-based particles can present a risk for protein aggregation.

Prefilled baked-on silicone glass syringes represent a marked improvement over transfer syringes with respect to particle loads. However, high numbers of 1 to 10 μm silicone oil droplets are present in these syringes and can present a risk for protein aggregation as seen in Figure 5. The particles between 1 and 10 μm, while not directly relevant to USP $<789>$ limits, nevertheless have the potential to affect protein stability—especially with agitation that may be experienced during shipping or at the time of injection. Although the clinical consequences of such subvisible particles are not well understood, it has been hypothesized, for example, that aggregates could be associated with the sustained increase in intraocular pressure.[23]

Silicone-oil-free and lubricant-free COP syringes are associated with the lowest particle loads in this study and show lower propensity for bevacizumab aggregation, likely because of the low surface energy of the COP material and the absence of a lubricant.

Considering the chronic nature of neovascular retinal diseases, the repeated injections delivered over the lifetime of the disease treatment, and the confined nature of the vitreous, the clinical consequences of injecting particulate matter, even subvisible particulate matter, may be cumulative. Silicone oil droplets because of their round shape are expected to be relatively easy to detect in the vitreous, and they are known to be present at high levels in insulin and other siliconized transfer syringes. They are therefore the first easy and obvious improvement to address with respect to the safety of intravitreal injections. The oleamide-lubricated plastic transfer syringe is likely

well-suited for withdrawal from a vial and immediate injection, but may have increasing subvisible particle counts with drug storage over time potentially leading to visible particle formation. Amorphous oleamide particles may or may not present as floaters, but could nonetheless present challenges with respect to meeting the particle requirements in the FDA's guidance: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application. Such transfer syringes may also have difficulty meeting some other requirements in the FDA biologics repackaging guidance which will be the subject of a subsequent study.

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NORM-JECT is a registered trademark of Henke-Sass, Wolf GmbH.

FlowCam is a registered trademark of Fluid Imagining Technologies, Inc.

Key words: 503B, anti-VEGF, bevacizumab, insulin syringe, intravitreal injection, oleamide, particles, prefilled syringe, protein aggregation, syringe, silicone oil, transfer syringe.

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