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PDA J Pharm Sci and Tech **2017**, 71 379-392

Access the most recent version at doi:[10.5731/pdajpst.2017.007724](https://doi.org/10.5731/pdajpst.2017.007724)

TECHNOLOGY/APPLICATION

Particulate Generation Mechanisms during Bulk Filling and Mitigation via New Glass Vial

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ABSTRACT: Contamination with foreign particulate matter continues to be a leading cause of parenteral drug recalls, despite extensive control and inspection during manufacturing. Glass is a significant source of particulate matter contamination; however, the mechanism, source, and quantification have not been extensively analyzed. Quantification of particulate matter generation with lab simulations suggests that glass-to-glass contact on the filling line produces large quantities of glass particles of various sizes. A new strengthened glass vial with a low coefficient of friction surface is proposed to address this root cause of glass particle generation. Lab simulations and two line trials using this new vial demonstrated a substantial reduction of glass particulate generation, of resulting product contamination, as well as of the frequency of required filling line interventions. These results suggest that substantial reductions in particulate matter contamination of all types, glass and non-glass, can be achieved through the use of a new glass vial designed to effectively eliminate a root cause of glass particle generation.

KEYWORDS: Particulate matter, Particle, Glass vial, Filling line, Low-COF surface, Glass contamination.

LAY ABSTRACT: Contamination with foreign particulate contamination continues to be a leading cause of injectable drug recalls, despite extensive control and inspection during manufacturing. Glass particles are one of the most common types of particulate identified; however, the generation mechanism has not been extensively studied. Lab simulations suggest that routine glass-to-glass contact of vials during the filling process results in large quantities of glass particulate. A new, strengthened glass vial with a low coefficient of friction surface is proposed to address this mechanism. Lab simulations and multiple filling line trials demonstrated a substantial reduction of glass particulate matter generation and product contamination with use of the new vial. These results suggest that this new vial reduces contamination risk by eliminating a root cause of glass particulate generation.

Introduction

The presence of foreign particulate matter contamination in parenteral drugs poses risks to patients and continues to be a leading cause of drug recalls (1–4). Recent medical risk-based approaches for assessing the presence of a low quantity of particles in the drug product conclude that the overall risk can vary considerably based on factors such as patient health, nature of the particle, and route of administration (3, 4). For low-risk routes of administration (subcutaneous and intramuscular) of a drug into a healthy patient,

clinically meaningful harm due to a few visible, sterile particles is considered to be unlikely (4). In contrast, neonates, infants, elderly, chronically sick, and immune-compromised patients injected intravenously are more vulnerable to the medical effects of such particulate contamination (3, 4). Documented clinical adverse effects in patients who have received injections containing foreign particulate matter contamination include phlebitis, pulmonary emboli, pulmonary granulomas, immune system dysfunction, pulmonary dysfunction, infection, and death (1, 3–10). As further evidence, use of inline filters for intravenous injections has demonstrated efficacy for capturing particles and has been linked to improved outcomes in high-risk situations (7, 9–11).

While the industry has largely focused on visible foreign particulate contamination, it has been suggested that subvisible particles may pose a greater risk

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doi: 10.5731/pdajpst.2017.007724

due to their smaller size and greater abundance (3, 4). Specifically, rigid subvisible particles greater than the size of the pulmonary capillary (10–12 μm) can be occlusive if intravenously injected and pulmonary microembolisms can cause impaired oxygen transfer and compromised respiratory function (4). Drug product conforming to compendial limits can and generally do contain measurable quantities of subvisible particles (3). In general, particles in this size range are more difficult to inspect and control due to technical limitations. Because the significant range of potential medical risks, lack of controlled studies, and technical limitations with inspection, assessing the risks associated from particle contamination continue to be a topic of considerable debate. Nonetheless, there is general agreement in the industry that the ultimate goal is zero tolerance for foreign particles in parenteral drugs and manufacturers should pursue continuous improvements to achieve this goal (4).

USP has set standards for foreign particulate matter levels in parenteral drugs. USP chapter <1> requires that drug products be “essentially free” from visible foreign particles, with acceptable monitoring methods and strategies provided in USP <790>. Visible foreign particulate matter is described as particles observable by a trained operator under specified lighting conditions without any further optical aids. Although no specific size range is provided, a threshold of 50 to 150 μm is typically assigned based on a moderate probability of detection (3, 12). Allowable levels of subvisible particles are defined in USP <788>. For small-volume parenteral drugs, up to 600 subvisible foreign particles $>25 \mu\text{m}$ and up to 6000 subvisible foreign particles $>10 \mu\text{m}$ are allowed. For protein therapeutic parenteral drugs, USP <1787> recommends monitoring particles in the 2–10 μm range as a potential quality indicator. Although measurement techniques and protocols have improved, the standards have remained largely unchanged since being proposed in 1936 (visible) and 1975 (subvisible) (3, 13).

In order to produce a safe product and to comply with these requirements and standards, manufacturers utilize extensive equipment, controls, and protocols to minimize contamination during the filling process. Product is also thoroughly inspected at the end of the line to ensure safety and quality. In spite of these efforts, foreign particulate matter–related recalls continue to increase (1). In fact, 22% of recalls for sterile injectable drugs in the period of 2008–2012 were due to the presence of visible particles, according to the

U.S. Food and Drug Administration (FDA) (2). In addition, industry survey results from 2014 indicate that foreign particles are the most common defect found during visual inspection, and glass particles are one of the most common contaminants of parenteral drug products (2, 3).

The FDA’s current good manufacturing practice (cGMP) regulations reflect the principle that “quality should be built into the product, and testing alone cannot be relied on to ensure product quality” (14, 15). While manufacturers are focused on extensive inspections for foreign particulate matter contamination and on assessing the medical risks, the root causes of such contamination, especially subvisible, are not always completely understood. Therefore, it is important to try to understand the root cause and explore new materials and methods that substantially reduce particle contamination and improve the quality of drug products.

While glass particle generation and contamination risks on filling lines due to vial breakage is generally understood, a less appreciated source of particles is the systematic glass-to-glass contact between vials during the filling process. This paper provides details of the glass-to-glass contact mechanism and suggests a new strengthened glass vial with a low coefficient of friction (low-COF) surface to eliminate this and other mechanisms of particle generation. The motivation for studying this mechanism was threefold: (a) particles are widely found in drug product and can cause serious health impacts and drug shortages in certain situations; (b) this mechanism hasn’t been extensively studied to date and therefore the magnitude and implications may not be clear to the industry; and (c) with contemporary technology, it was possible to design a new glass vial that can substantially reduce said particulate generation and drug product contamination in the filling process and therefore the associated risk to patients.

Filling Line and Vial Damage Characterization

Conventional vial filling lines comprise of washing, depyrogenation, filling, stoppering, and capping operations enclosed in a clean and utmost controlled environment. Isolator or restricted access barrier technology with high-efficiency particulate air (HEPA) filtration is commonly adopted to provide an environment with the highest levels of sterility assurance. Downward laminar airflow is incorporated into the barrier or isolator lines and is designed to sweep particles away from the containers to minimize con-

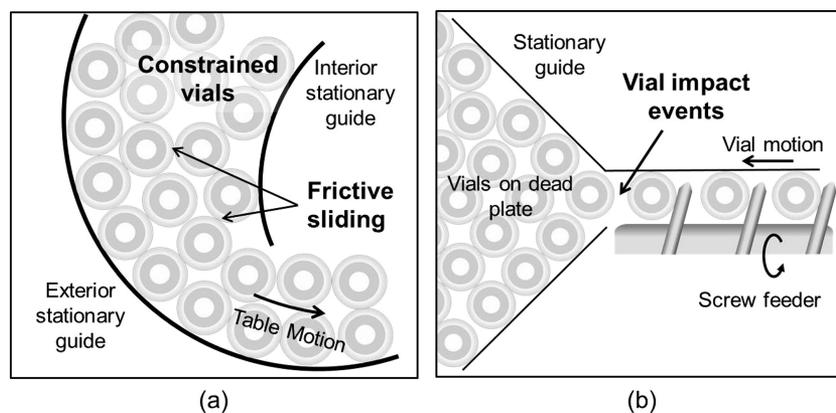


Figure 1

Exemplary images of frictive sliding and impact interactions found on filling lines. (a) Vials in motion slide past vials constrained by the inner guide on a rotary accumulator table. (b) A screw feeder accelerates and impacts vials into a large quantity of stationary vials on a dead plate.

tamination (14). Inside this controlled environment, however, vials are conveyed using methods that rely on systematic glass-to-glass contact. Although filling line handling methods vary, vial-to-vial interactions on the line can generally be classified as frictive sliding or impact events. The nature of the interaction contributes to the damage and the primary particle generation mechanism.

Frictive sliding, where two vials slide past each other (Figure 1a), is more predominant and severe during bulk handling. Bulk handling on the filling line utilizes wide belts or moving/turning tables for loading, depyrogenation, and accumulation operations. In this mode of handling, large quantities of vials are constrained by stationary guides, resulting in low-speed interactions; however, the forces generated can be relatively large due to the large collective vial mass. The combination of low speeds with high forces applied to vials that are already in contact with each other results in largely frictive sliding interactions.

Vial-to-vial impact interactions are more common and severe during singulated conveyance (single-file) or during transitions between singulated and bulk handling modes. Transition operations, such as starwheels and screw feeders, accelerate vials often into other stationary or slow moving vials (Figure 1b) resulting in vial-to-vial impacts. Bulk conveyer loading onto an accumulator table is another location where impact interactions are dominant. In these cases, higher velocities result in frequent and severe impacts between vials indicating that the increased energy of impact

event is an important contributor to particle generation.

Characteristic surface damage from each of these interactions was observed via optical inspection of conventional 3 mL glass vials that were processed on a bulk vial filling line. Frictive sliding interactions produce surface scratches with a characteristic roughened appearance. Of the hundreds of samples inspected, this type of damage was observable on every vial and ranged in size from several microns to visible scratches. Glass chatter checks (localized surface fractures) were also observed regularly and often associated with more severe damage (Figure 2a). In 8% of vials inspected, an obvious chip >120 μm was found on the glass surface, where chatter checks extended to the surface (Figure 2b). Further characterization of the damage by optical interferometry revealed that the frictive damage actually penetrated the surface by as much as 6 μm (Figure 3a). Similarly, holes left behind by glass chips were found to be up to 20 μm deep (Figure 3b). During inspection, the ability to easily remove complete chips from damage sites demonstrates that glass chips of this size can remain intact upon ejection. In all of these cases, missing material from the surface is evident.

Glass surface damage from mechanical contact, representative of glass-to-glass contact between vials on a filling line, is a common subject in the field of indentation fracture mechanics (16–19). In this field, model systems are used to characterize the stress field and crack formation, and to predict the strength reduction.

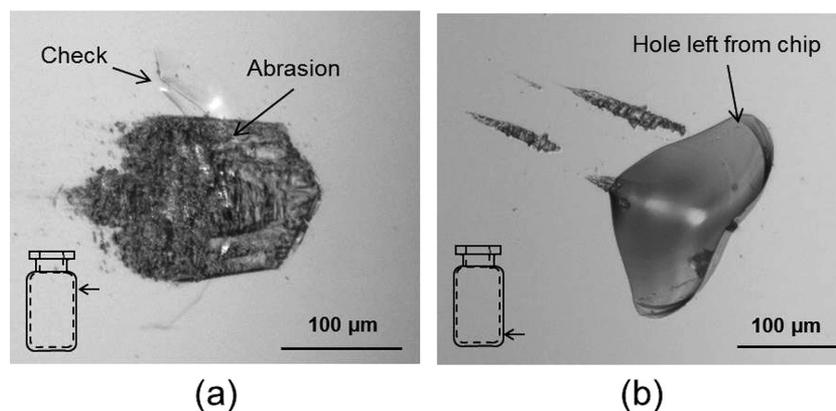


Figure 2

Representative damage on the surface of a glass vial processed on a conventional bulk filling line. Abrasion, chatter checks (a), and missing glass chips (b) are a result of glass-to-glass contact.

Although the surface morphology or particulate generation has not been a principal area of focus, understanding check formation and surface stress generation is relevant to these mechanisms. Le Houerou studied glass surface damage while translating a Vicker's indenter across a glass surface (16). At the highest loads, a micro-abrasion regime is observed where the applied stress exceeds the local strength of the material. At the contact area, the applied stress

causes extensive micro-fracturing and particulate generation resulting in a roughened surface. This observation appears consistent with the frictive sliding damage observed on processed vials.

In his work with sliding blunt indentation systems, Lawn calculates tensile loads in the trail of a scratch that can lead to crescent cracks similar to damage from frictive sliding (18). The evolved tensile forces in the

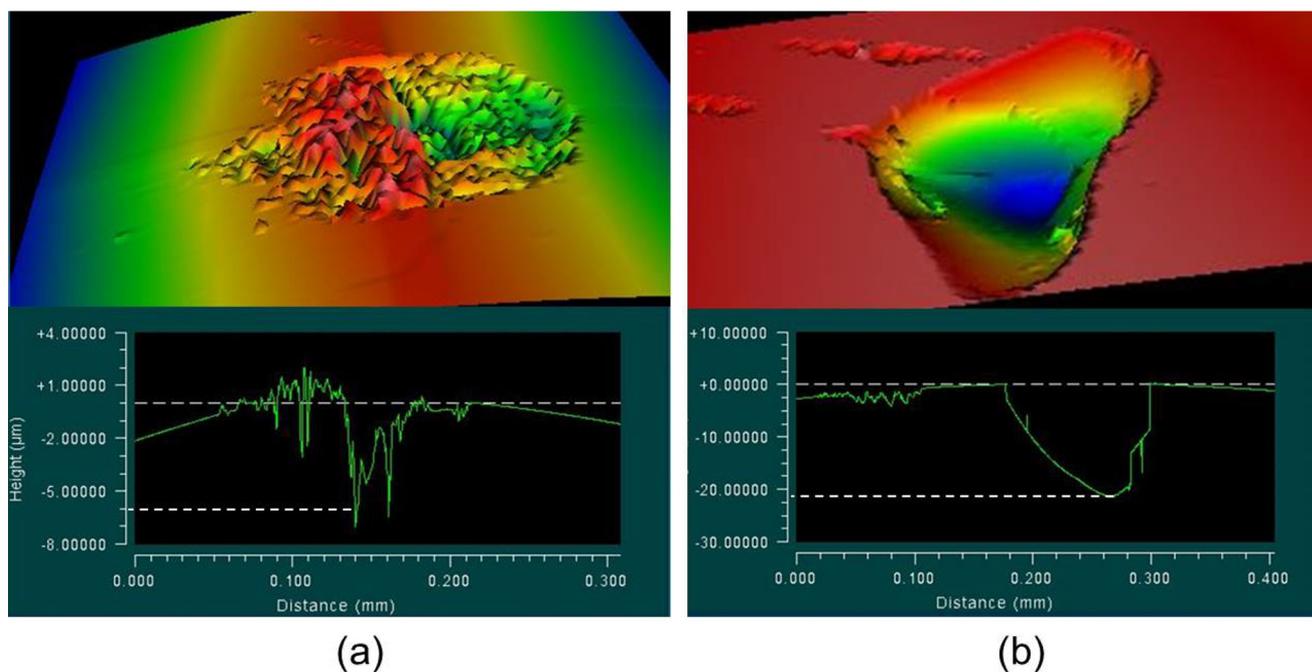


Figure 3

Optical profilometry and cross-section of glass surface damage from Figure 2. (a) Abrasive damage with maximum depth of 6 µm; (b) missing glass chip with 20 µm depth.

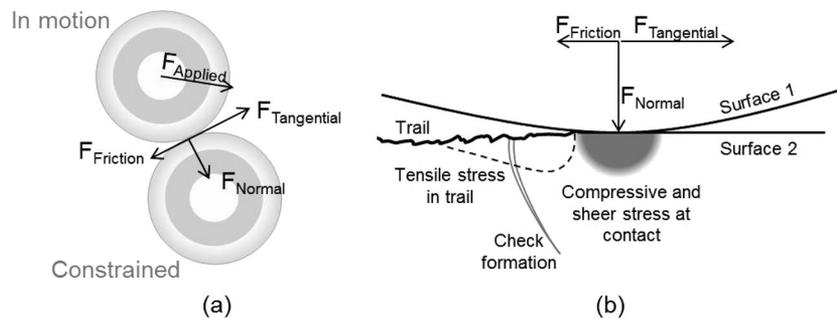


Figure 4

Illustration of the forces and stresses generated during sliding contact between vials macroscopically (a) and microscopically at the surface (b). The magnitude of the tensile stress and shear stress are both proportional to the COF between the materials.

trail, and stress fields in the contact region, are both proportional to the applied load and the COF between the materials (Figure 4). As compared to many material systems, the COF between clean glass surfaces is particularly high. Prior to entering the isolator or barrier portion of the filling line, vials are typically sterilized by dry heat depyrogenation, resulting in an extremely clean surface with a COF ranging from 0.9 to 1.0 (20). As a reference, this level is comparable to that of a tire on a road under dry conditions (21). This high COF level results in proportionally high localized contact (shear) stresses and tensile stresses, which are ideal conditions for particulate generation.

Glass Particles on the Filling Line Results from Multiple Mechanisms

Based on understanding the vial interactions on the filling line, the resulting surface damage, and the underlying fracture mechanics, two mechanisms for glass particle generation are proposed: frictive sliding contact and impact events. Glass delamination is an additional mechanism of particle generation, but is not considered in the scope of this work.

Frictive Sliding Contact

Frictive sliding contact between vials results in surface stress at the contact location. When the surface stress exceeds the local material strength, the glass will fracture and produce extensive particles. The generated particles can further intensify the local stress by reducing the contact area. This mechanism is comparable to the abrasion of materials caused by polishing or grinding and, as will be shown, results in significant generation of subvisible particles (<50 μm).

Impact Events

Based on optical inspection, visible particles (>100 μm) appear to be generated via a different mechanism. In this case, tensile stress on the glass surface results in the propagation of a microscopic surface flaw, transforming it into a larger macroscopic check, depending on the orientation and magnitude of the tensile stress and the check geometry, the check direction can turn and/or continue to propagate. If the check propagates and converges into a nearby check or to the glass surface, a glass chip can be released from the surface. This mechanism could result from a single or multiple applications of tensile stress from various interactions. While tensile stress and checks are generated during low speed frictive sliding interactions, it is hypothesized that increased energy and higher tensile stresses increase the probability of this mechanism occurring during impact events.

While each of the mechanisms described above can result in particle generation without causing complete container breakage, it is understood that complete container breakage can also lead to generation of particles in all size ranges.

Lab Evaluation of Particle Generation from Each Damage Mechanism

To study the quantity and size distribution of glass particles generated, laboratory simulations of vial interactions on the filling line were conducted. Based on the optical inspection results, it was hypothesized that the frictive sliding contact and impact events could generate different types of damage and glass particle sizes. In order to develop tests with relevant force

levels and speeds, multiple filling lines were characterized. Forces between vials were probed using a thin film load cell (Tekscan Flexforce). The sensor was inserted between vials during typical operation on accumulator tables and other accessible regions where contact occurs. Peak forces as high as 30 Newtons (N) were observed with typical loads ranging from 2 to 10 N. High-speed video was also used to determine maximum instantaneous vial velocities. Vial velocities of up to 400 mm/s were recorded. This information was used to create laboratory simulations for each type of interaction that show damage consistent with that observed on conventional glass vials following the filling process.

Frictive Sliding Contact Simulation

A method was developed to simulate glass vial frictive sliding contact and reproduce damage observed from bulk glass vial handling. In this method, two glass vials are oriented orthogonally in a fixture with contact between the vial side walls. A mechanical tester applies a controlled, constant load and translates one of the vials linearly. The translation direction is 45 degrees relative to the barrel direction in order to produce a scratch on pristine surfaces of each vial. During the scratch generation, glass particles are ejected to a nearby particle debris field. The debris field is microscopically inspected and the glass particles automatically counted using vision software.

Conventional 3 mL borosilicate glass vials were depyrogenated and tested with an applied load ranging from 1 to 30 N over 1 mm scratch length. Representative images of the damage and the associated debris field illustrate similar abrasion and surface checks to filling line processed samples (Figure 5). As would be expected, the size of the damage site, the debris field, and the severity of glass checks increase with higher loads.

Optical images of the debris fields were captured and analyzed by imaging software to determine glass particulate distributions for 15 pairs of scratched vials as a function of load (Figure 6). The distribution contained glass particles primarily less than 10 μm ; however, glass particles between 10 and 50 μm were also observed (Figure 7). The total quantity of glass particles observed in the debris field ranged from approximately 700 to 1800 particles per 1 mm scratch as a function of the load. As described later, this repre-

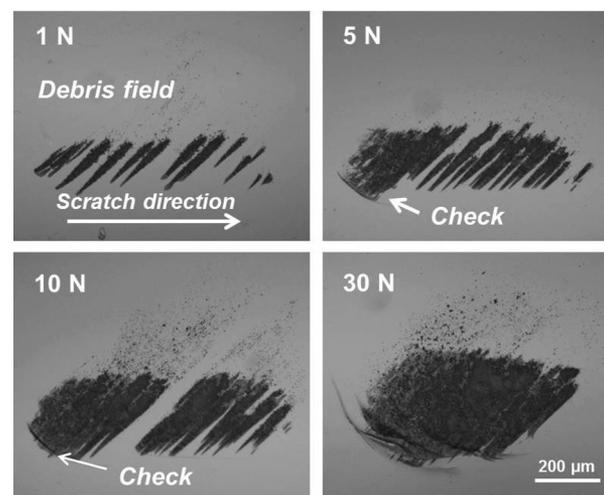


Figure 5

Images of surface damage and debris field associated with frictive sliding contact with 1 mm scratch at various loads. Glass checking is also observed at the initiation of the scratch.

sented only a portion of the total number of particles generated.

The effect of translational scratch speed was also examined over the range of 6 to 120 mm/min to simulate different velocities of vial interactions. Results showed that at a constant applied load (30 N) the morphology of the damage site and subsequent glass particulate distributions did not vary markedly with the change in speeds (Figure 8), suggesting that the

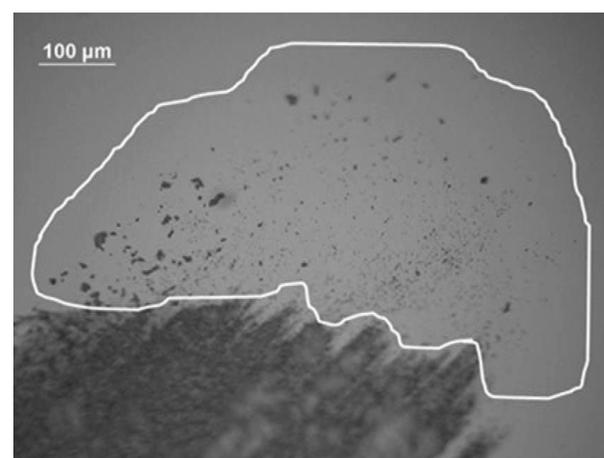


Figure 6

Exemplary debris field generated during frictive sliding simulation at 10 N. The area outlined in white is analyzed by particle counting software.

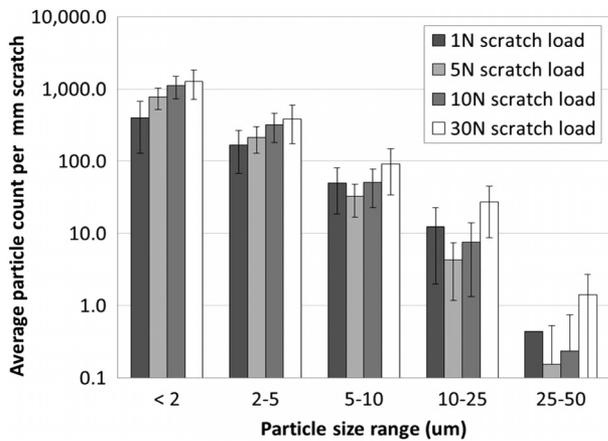


Figure 7

Glass particle distribution following a 1 mm scratch at 60 mm/min. Total particulate generation ranged from 1800 particles/mm scratch at 30 N to 700 particles per/mm scratch at 1 N. Little difference in the glass particle distribution is observed between loads.

glass particle size distribution is independent of both applied load and speed over the range evaluated.

In order to better assess the total quantity of glass particles generated, damage sites were also imaged by scanning electron microscopy (SEM). Representative images of damage sites produced from a 1 N load applied reveal jagged and irregular glass particles, consistent with those particles identified optically

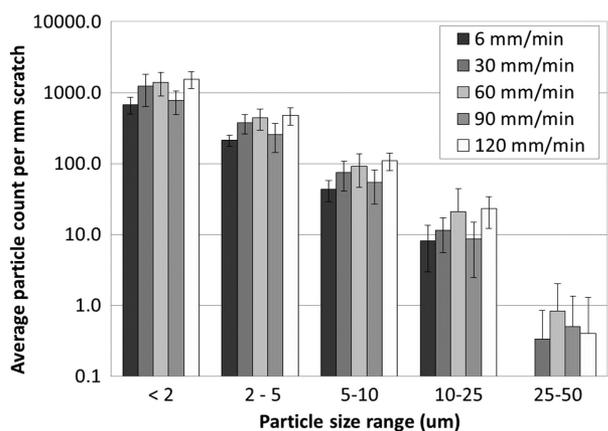


Figure 8

Glass particle distribution following a 1 mm scratch at 30 N. Little difference in the particle distribution is observed between speeds of 6 to 120 mm/min.

(Figure 9). Qualitative assessment of the SEM images indicated that the majority of the glass particles remained at the damage site versus being ejected to the debris field, indicating that the debris field particles represent only a portion of the total glass particles generated. No significant difference in particle or damage site morphology was found over the range of loads tested. Furthermore, these glass particles were found to be easily removed from the surface of the vial via lightly blown air or physical contact by a swab. The ease of removal suggests that the glass particles generated as a result of glass-to-glass contact during filling are likely released immediately into the filling environment.

To estimate the total number of particles generated, optical profilometry of scratch sites, similar to technique used to generate images in Figure 3, was used to quantitatively determine the efficiency of particle collection in the debris field. The volume of glass lost from damage sites was measured and compared to an estimated volume of total particulate observed in the debris field. This analysis indicated that only ~30% of particles are being ejected to the debris field, suggesting that the actual quantity of particles generated could be as high as ~6000 for a single 1 mm scratch.

This laboratory study confirms that frictional sliding contact, which is ubiquitous on traditional sterile filling lines, is a significant source of glass particulate generation. Furthermore, based on the number of defects found during inspection, the quantity of glass particles generated from a conventional 3 mL glass vial during a typical filling-line campaign can range from tens to even a hundred thousand particles per vial.

Impact Event Simulation

Dynamic impact testing was performed to simulate vial impact events that occur on the filling line and to determine if the generated glass particle size differs from those observed with frictional sliding contact. A dynamic test system was developed that enables a single vial to be accelerated toward a constrained stationary vial at a controlled velocity. With this system, the vial in motion is fixtured with an air-bearing piston such that the vial can freely recoil upon impact and the associated momentum from the fixture is minimized. The degree of frictional sliding between vials was controlled by adjusting the compliance of the stationary vial fixture, thus enabling impact simula-

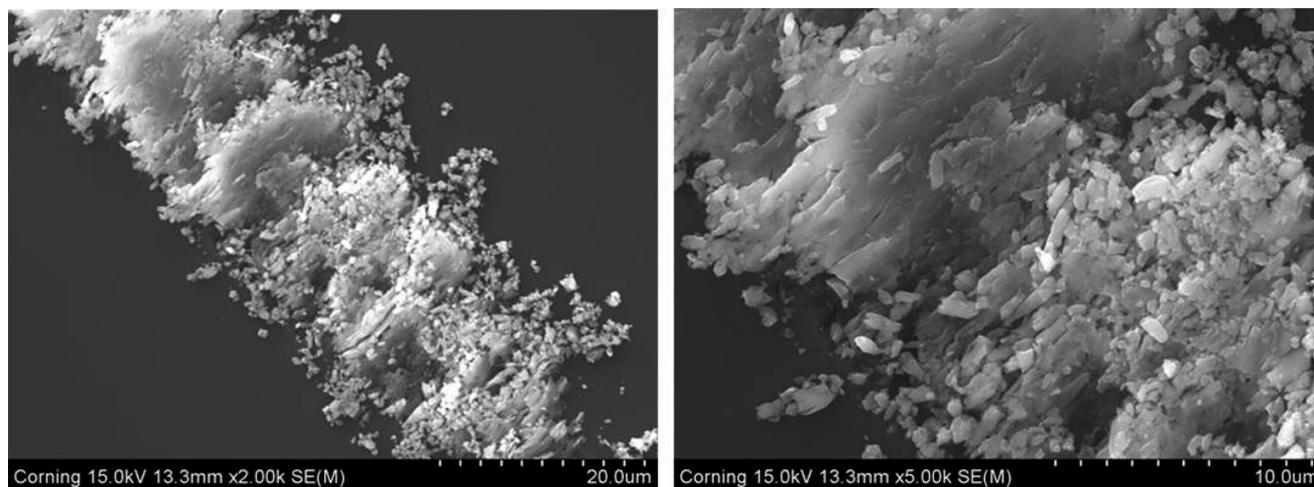


Figure 9

SEM images of damage site produced using frictive sliding contact test (1 N load). A number of glass particles remain in the damage area following the scratch.

tions of a fully or partially constrained vial on the filling line. To simulate the COF of vial surfaces on the filling line, vials were depyrogenated immediately prior to testing. Impact velocities ranged from 400 to 1000 mm/s, representing an upper range of instantaneous speeds observed on the filling line.

A variety of factors were evaluated in order to simulate the range of impact interactions that are possible during the filling process. These factors included the impact velocity, vial orientations (contact area), amount of frictive sliding, and the presence of preexisting damage. Particle generation during impact was recorded by high-speed video. Generated particles did not reliably deposit in a predictable location making precise quantification impractical. Consequently, key findings are reported based upon the qualitative observations of particle generation and damage severity.

Initial experiments were completed with impacts between pristine surfaces in which frictive sliding was prevented (fully constrained vial). In these cases, damage sites were small and particulate generation of any size was difficult to detect. As the amount of frictive sliding increased during impacts, abrasive damage was observed similar to that observed in the frictive sliding simulation. Ejected particulate was predominately $<50\ \mu\text{m}$ as estimated in the high-speed video.

The imparted surface stress was increased by adjusting the vial tilt to minimize the contact area and by increasing the impact velocity. By increasing stress and

energy during the impact (by controlling velocity), the predominance of surface checks (precursor for visible particles) also increased. Despite the increased severity of the impact however, ejection of visible glass particulates ($>100\ \mu\text{m}$) from a single impact between pristine surfaces was observed in less than 1% of the tests.

However, the presence of preexisting damage at the impact site markedly affected the frequency of visible glass particle generation. Preexisting damage was introduced by multiple impacts in the same location. In subsequent laboratory testing, the frequency of particles $>100\ \mu\text{m}$ being ejected increased to approximately 10%, a $10\times$ increase over pristine impacts under the same conditions. Although the frequency and magnitude of impact events and subsequent particle ejections will vary as a function of filling line design and setup, the increased frequency of ejected visible particles from multiple impacts is consistent with the previously mentioned observation that 8% of inspected vials showed evidence of a check (and corresponding visible particle generation) greater than $120\ \mu\text{m}$.

In some instances, a visible particle was generated and ejected from the interior surface of the vial upon impact; however the vial remained intact (Figure 10). This particular type of impact event could result in certain contamination of the product by a visible particle and could occur after inspection.

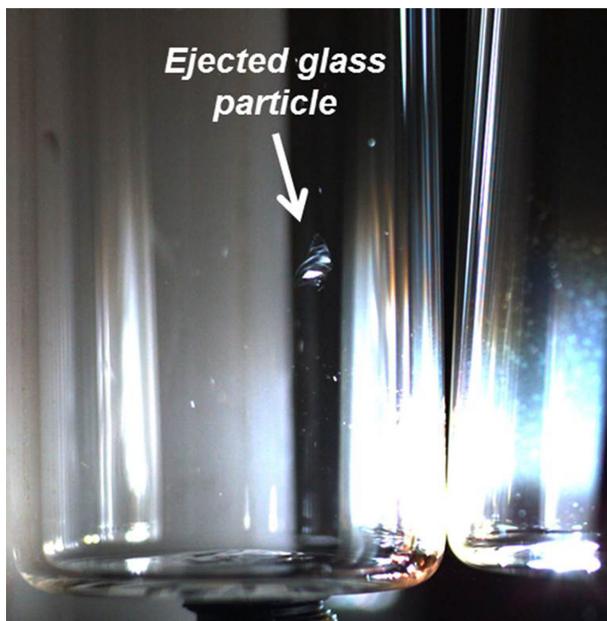


Figure 10

Image capture of high-speed video illustrating visible glass particle ejection during impact testing. The size of the particle is $>100\ \mu\text{m}$.

As expected, increasing the surface stress and energy of the impact increases the severity of damage and frequency of checks. For pristine surface impacts, frictive sliding results in generation of primarily sub-visible particles. Preexisting damage prior to an impact significantly increases the propensity for visible glass particles ($>100\ \mu\text{m}$) to be generated. Inspection of the filling line processed vials indicates the presence of such surface damage. Although the frequency of visible glass particle generation depends on many factors including the line design, setup, and operation, glass damage and impact events are unavoidable in current filling operations, posing a risk to particulate generation by this mechanism.

Importantly, this simulation also demonstrates that vial breakage is not required to produce visible glass

particles on the filling line, confirming the existence of a significant, but less obvious, glass particulate generation mechanism.

New Vial Designed To Address Root Cause of Particulate Mechanisms

With knowledge of the particulate generation mechanisms, we propose a new glass vial to substantially reduce glass particulate generation on vial filling lines by the aforementioned mechanisms. This vial leverages existing technology used for other contemporary glass products today such as optical fiber, cell phone covers, and display glass applications. The new vial is made from an aluminosilicate glass composition described previously (22). To mitigate particle generation mechanisms, the vial includes a low-COF exterior surface and is chemically strengthened. The new vial is described further in Table I.

A key advantage of the low-COF surface is the prevention of abrasive surface damage during frictive sliding contact. In addition, it is hypothesized that it also minimizes transfer of the tensile stress to the glass surface required to form or propagate checks. The glass is strengthened by imparting a compressive stress on the surface of the glass. This surface compressive stress could create an additional barrier to check formation and propagation and suppress formation of visible glass particles. The strengthening also improves the overall vial robustness, reducing the probability of breakage from high stress loading and particulate generation from fragmentation.

Furthermore, the new vial was designed to be fully compatible with mechanical and chemical requirements of the industry, including typical depyrogenation cycles. The vials meets type I hydrolytic performance requirements per USP $<660>$. It was designed to run on existing filling lines without requiring any modifications to the line or equipment.

TABLE I
Comparison of New and Conventional Vials

	Conventional Vial	New Glass Vial
Glass material	Borosilicate (unstrengthened)	Aluminosilicate (strengthened)
Vial format/size	ISO 2R, 3 mL	ISO 2R, 3 mL
Glass type (per USP $<660>$ test)	Type I	Type I
Exterior COF (post depyrogenation)	0.9 to 1.0	<0.5

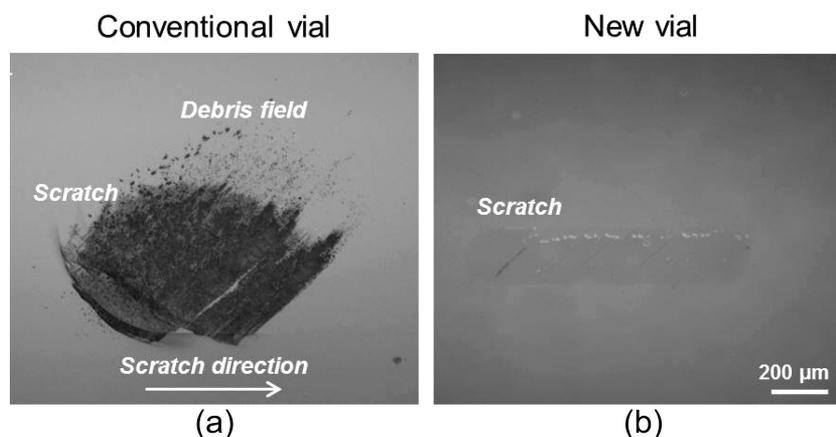


Figure 11

Optical inspection of surfaces following 30 N scratch test. Significant damage and checks are observed on the conventional vial (a) while no glass damage is present on the new vial (b).

Line Trials Using the New Vial Demonstrate Substantial Reduction in Particle Risk

Initial testing of the new vial with the low-COF surface was performed with abovementioned laboratory tests to evaluate performance during frictive sliding and impact interactions, as compared to conventional borosilicate vials. Evaluation in both frictive sliding (Figure 11) and impact tests showed no observable glass damage or particle generation. Impact testing also confirmed effective elimination of frictive glass scratches, surface check formation, and subsequent particle generation over the range of conditions evaluated.

Following laboratory evaluation of the new vial, two filling line trials were undertaken to quantify the particle reduction benefit in the filling line environment. The first trial comprised of processing approximately 1 million 3 mL vials on a high-speed restricted access barrier-style filling line with an experimental protocol specifically assessed airborne particulate matter response (performed on a production filling line at a manufacturer not affiliated with Janssen). This continuous line consisted of conventional operations (wash, depyro, fill, stoppering, capping) and environmental controls with accumulator tables prior to washing and following the depyrogeneration conveyer. Inline monitoring of airborne particulate matter near the post-depyrogeneration rotary accumulator table (~45 in diameter) within the barrier was performed using airborne particle monitors (Airnet 510 XR I, sensitive to particles 0.5 µm or greater). For this trial, >5 um airborne particle counts and container particle counts

were not available for analysis. The line was operated using typical production protocols and setpoints with an operating speed range of 500 to 550 vials/min. In addition, a detailed record for each operator intervention was also maintained. The results were then compared to a conventional glass vial that was run immediately before the new vial, using the same protocol and similar quantity of vials. A standard line cleaning was performed prior to each run.

While processing conventional glass vials on the filling line, frequent operator interventions were required to alleviate jammed, tipped, or broken vials or to clean specific container guide surfaces. Interventions elevate the contamination risk of all airborne particulate matter by disrupting the laminar flow and by disturbing settled particles (14). When running the new glass vial with the low-COF surface, the machinability improved significantly, as evidenced by a 61% reduction in interventions and a 36% increase in effective line throughput. Line lubrication and in situ surface cleaning, typically used at key locations during filling line operation, were not performed, suggesting an overall lower level of particulate generation than what is traditionally experienced during a filling campaign. Furthermore, particulate matter monitoring showed a 96% reduction in peak particle levels (>0.5 µm particles) above the post-depyrogeneration accumulator table, where vials are open and at risk to foreign matter contamination. This result demonstrated that, by mitigating the generation mechanism and reducing interventions, airborne particle levels, which are an important indicator of overall particle contamination risk,

TABLE II
Comparison of Particulate Performance Metrics for Trial 1

	Conventional Vial	New Vial	% Reduction
Particle count range (0.5 $\mu\text{m}/\text{m}^3$)	114–8609	100–337	96% (peak level)
Total particle spikes	59	36	39%
Particle spikes at in-feed	50	4	92%
Interventions	247	95	62%

can be substantially reduced during the filling process. Results for this line trial are summarized in Table II.

A second line trial of the new glass vial was conducted by a different pharmaceutical manufacturer on an isolator-style line with explicit focus on assessing the overall particle reduction benefit. Similar to the previous trial, this line consisted of standard filling operations including a larger rotary accumulator table following the depyrogenation conveyer exit. The line was fully enclosed with HEPA-filtered downward laminar flow and glove ports for access. The line was operated between 200 and 278 vial/min with standard production protocols and setpoints. In this trial, ~ 8000 ISO 2R vials of each vial type were processed normally. Both the new vial and control vial (conventional) were made with the same dimensions. Airborne and surface particles in the isolator and in-solution particles were all monitored. In order to monitor the environment at the vial processing level, supplemental airborne particulate matter monitoring in the isolator was accomplished using 4 inch silicon wafers as settling plates. The wafers were placed at various locations, including the post-depyrogenation accumulator table, the depyrogenation tunnel entrance, and the washing area, at the same elevation as the vial openings. Surface particulate matter monitoring was completed by wiping surfaces with adhesive carbon tape and performing SEM analysis prior to and following each trial. Targeted surfaces in-

cluded accumulator table surface, guides, and the screw feeder. Particle monitoring via wafers and carbon tape sampling was performed without opening the isolator. Particles in the solution were assessed by light obscuration according to USP <788> with samples from the beginning, middle, and end of the trial. The isolator portion of the line was cleaned using standard protocols prior to the trial of each vial type.

Compared to the control run with conventional glass vials, the trial with the new glass vial showed an 85% reduction in airborne particles near the accumulator table, as indicated by the wafer settling plates. The collected particles ranged in size from 20 to 120 μm and, based on a qualitative optical inspection, the particles were found to be a mix of both glassy and organic types.

No differences in visible particle contamination were observed in the solution for the two different vial types; however, a substantial reduction (42–50%) was seen in average subvisible particle levels within the solution for the new vial in all three particle size ranges evaluated as detailed in Table III. Based on the standard deviation levels, a clear reduction in the two smaller size ranges is observed; however, the difference in particle levels for the >25 μm range is not statistically significant. The results from the wafer settling plates, combined with mechanistic under-

TABLE III
Comparison of Particulate Performance Metrics for Trial 2

	Conventional Vial	New Vial	% Reduction
Airborne particle count (wafer settling plate)	156	23	85%
Solution particle counts (2–10 μm)*	1318 \pm 136	761 \pm 68	42%
Solution particle counts (>10 μm)*	28 \pm 6.9	14 \pm 2.9	50%
Solution particle counts (>25 μm)*	0.42 \pm 0.52	0.23 \pm 0.17	45%
Interventions	15	3	80%

* Measured using light obscuration. Average of 20 samples from beginning, middle, and end of trial, average and standard deviation of number of particles/container reported.

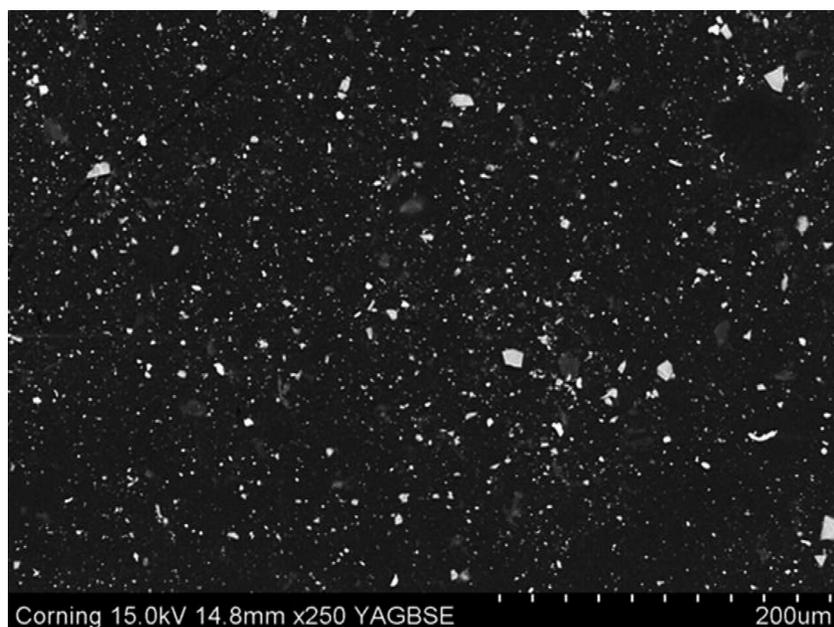


Figure 12

SEM images of carbon tape contamination found following the line trial with the conventional vial. A significant quantity of glass particles were observed ranging in size from 1 to 15 μm .

standing, suggest that reduction in all ranges could be expected; however, the low baseline level in the >25 μm range makes discrimination difficult in this case. Consistent with the previous trial, operator interventions were also reduced by 80%, which is another contributing factor to the particle level reduction (of all types). Results for this second trial are summarized in Table III.

These results further confirm that glass-to-glass vial contact is a significant source of particles. They also suggest that standard environmental controls such as vertical laminar airflow are not completely effective at preventing particles generated on the line from entering the vial. It is hypothesized that, even in well-designed isolator systems, horizontal surfaces of the equipment (e.g., conveyer surfaces) and even the bottom of the vial disrupt vertical laminar airflow that is intended to sweep away contaminants.

SEM inspection of the carbon tape from surface sampling revealed significant glass particulate matter contamination following the trial from the conventional glass vial, ranging from sub-micron to 20 μm for all areas evaluated (Figure 12). Quantification of particle distribution from the images is impractical; however, the observed range is consistent with particle distributions measured on the frictive scratch test. Composi-

tion analysis by energy dispersive X-ray spectroscopy (EDX) indicated that between 11% and 50% of particles collected were glass.

Despite the standard isolator cleaning protocol, carbon tape sampling prior to the line trial with the new vial indicated the presence of a considerable quantity of glass particles from the conventional vial. This was confirmed by EDX compositional analysis. It seems probable that some quantity of subvisible particulate matter detected during the trial with the new glass vial could be a result of the residual particulate contamination left on the line after the control trial run with conventional vials. Therefore, even greater particle reduction could be realized if the underlying base of conventional glass particles were fully removed.

The new glass vial is designed to be fully compatible with existing filling lines and it requires no changes to processing equipment. This was confirmed during the line trials as no line modifications were required beyond a typical line setup protocol.

Conclusions

Glass-to-glass contact of conventional type I borosilicate glass vials on filling lines is a significant source of foreign particulate matter contamination during aseptic

tic processing prior to container closure. This glass-to-glass contact significantly increases (by approximately 10×) the likelihood of generating visible glass particles and is a root cause of the generation of large quantities of subvisible glass particles on filling lines. In addition, the large quantities of glass particulate can increase the frequency of filling line interventions and the risk of contamination from all types of particulate.

Pharmaceutical manufacturers have an obligation to identify, understand, and control critical process factors (14, 23) and have implemented existing equipment, controls, protocols, and inspections to reduce the risk of foreign particulate matter contamination in a conventional vial. However, these steps do not fully address the root cause of the problem. Now that this root cause is more clearly understood, manufacturers can take action to mitigate the glass-to-glass particle generation mechanism described herein, which has been found to result in drug product contamination, and implement feasible solutions that build in quality.

A strengthened glass vial with a low-COF surface is one such solution. This new vial is designed to address the main root cause of both visible and subvisible glass particulate matter generation during the filling process. Two line trials have demonstrated a substantial reduction in both airborne (in isolator) and in-solution particle contamination. During the line trials, significant reduction in the frequency of required line interventions was also realized. Furthermore, line trials have confirmed compatibility with existing manufacturing equipment and processes. This study has demonstrated that, by understanding and addressing a root cause of a major foreign particulate matter source, a strengthened vial with a low-COF surface can substantially reduce said particle contamination and thereby have a positive impact on product quality and safety.

Acknowledgments

The authors thank Ronald Davis, John Bayne, Kyle Hoff, Jamie Morley, and Doug Noni for technical support.

Conflict of Interest Declaration

Christopher Timmons was employed by Corning Incorporated during execution of this research. Chi Yuen Liu and Stefan Merkle declare that they have no competing interests.

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