Enhancing patient safety through the use of a pharmaceutical glass designed to prevent cracked containers

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Technical Abstract:

An essential role of packaging material for the storage and delivery of drug products is to provide adequate protection against contamination and loss of sterility. This is especially important for parenteral containers, as lack of sterility or contamination can result in serious adverse events including death. Nonetheless, cracked parenteral containers are an important source of container integrity failures for injectable drugs and pose a serious risk for patients. Despite significant investments in inspection technology, each year many injectable drugs are investigated and recalled for sterility risks associated with cracked borosilicate containers. Multiple studies and the many difficulties in detection of cracked containers suggest that the magnitude of the public health risk is even larger than the recall rate would suggest. Here we show that the root cause of cracked parenteral containers (low internal energy following annealing) is inherent to the glasses currently used for primary packaging of the majority of injectable drugs. We also describe a strengthened aluminosilicate glass that has been designed to prevent cracks in parenteral containers through the use of an engineered stress profile in the glass. Laboratory tests that simulate common filling line damage events show that the strengthened aluminosilicate glass is highly effective at preventing cracks. Significant safety benefits have been demonstrated in other industries from the use of special stress profiles in glass components to mitigate failure modes that may result in harm to humans. Those examples combined with the results described here suggest that a significant improvement in patient safety can be achieved through the use of strengthened aluminosilicate glass for parenteral containers.

Lay Abstract:

Cracks are small cuts or gaps in a container which provide a pathway for liquid, gas or microbes through a glass container. When these defects are introduced to conventional glass containers holding injectable medicines, the affected drug can pose serious risks to the patient receiving that medication. Specifically, the drug product may become less effective or even non-sterile which could lead to bloodstream infections and, in some cases, death. This article presents a review of some previously-documented cases of cracked glass containers which led to patient infections and deaths. Following a survey of common crack locations in glass vials, lab-based methods for replicating these cracks are presented. These methods are then used to compare the fracture response of vials made from conventional borosilicate glass and strengthened aluminosilicate glass. The results show that stable cracks are essentially prevented (at least 31 times less likely to occur) in the strengthened aluminosilicate glass containers (relative to conventional borosilicate glass). This improvement in safety is similar to improvements already engineered into other glass product designs by utilizing stored strain energy to mitigate certain failure modes.

Introduction

The primary purpose of the container closure system for a parenteral solution is to provide protection for the dosage form in a safe and compatible manner. Each year, several billion injectable doses are delivered successfully around the world (in a variety of closure systems), providing lifesaving medications and preventing various diseases. US federal regulations require that the closure system must not be 'reactive, additive, or absorptive so as to alter the safety, strength, quality, or purity of the drug' and that it must 'provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product[1].' FDA guidance lists common causes of deterioration and contamination such as exposure to light, loss of solvent, exposure to reactive gases (e.g., oxygen), absorption of water vapor, and microbial contamination[2]. The pharmaceutical manufacturer must ensure that the chosen container closure system (e.g., glass vial + elastomeric stopper + aluminum crimp seal) provides this protection for the specific drug product in a suitable manner throughout its shelf life.

The failure of a container closure system to protect the drug product can have serious and even deadly consequences. Container breakage can result in a missed dose, lacerations, or drug shortages. Inadequate sealing of container closure components may allow liquid or gas transport (ingress or egress) resulting in an ineffective or adulterated dose[2]. However failures from cracked containers, sealing problems (improper assembly, sealing-surface defects, dimensionally incompatible components), and cored stopper materials are especially serious because they can provide even larger openings for biological material transport (ingress or egress). Injectable products require protection from microbial contamination because they bypass most of the body's natural defenses (skin, mucous membranes, etc.), permitting rapid and complete introduction of microbial contamination into a patient's circulation. Accordingly, these breaches in container closure can lead to bacteremia, fungemia, sepsis, or death[3-5].

Glass is an ideal material for parenteral packaging because it uniquely combines several properties that other materials cannot[6-7]. Glass containers are transparent, hermetic, non-porous, easily formed into complex shapes, chemically durable against a wide range of solutions, and resist deformation under applied loads. This unique combination of properties makes glass the material of choice for packaging injectable products[8]. Indeed approximately 98 percent (or 23 billion) of parenteral containers were packaged in glass in 2012[9]. The majority of these parenteral containers are made of Type I borosilicate glass.

One drawback of conventional glass containers (current borosilicate and soda-lime silicate containers) is that strength-reducing damage can be introduced during forming and handling. Cracks are one example of such damage and are defined as a "fracture that penetrates completely through the glass [container] wall[10]." They are classified as 'critical' defects, that are "likely to result in personal injury or potential hazard to the patient" because the nonconformity "compromises the integrity of the container, and risks microbiological contamination of a sterile package[10]." Figure 1 shows a photograph of a cracked vial associated with an outbreak of bloodstream infections due to cracked borosilicate glass[4].

There are many examples of cracks in glass containers observed during investigations of bacteremia and fungemia, spanning six decades. For example:

a) In January 1968, 5 patients experienced septicemia after receiving 5% dextrose in water solution following elective surgery. During the investigation, a small crack was observed in the base of a sixth glass bottle administered to a sixth patient[11].

b) Around 1970, a patient received approximately 200mL of a glucose-saline infusion before it was noticed that the bottle was cracked and contained clumps of green fungus[12].

c) In another case around 1970, a separate patient received an infusion of glucose-saline contained in glass that was cracked and contained white clumps of penicillium[12].

d) In 1972, mold was introduced to an intravenous solution through cracks in the glass from the gum adhesive on the back of its label[13].

e) In 1975, a bottle with cracks near its base was discovered because its solution was abnormally colored and slightly turbid, yet none of the fluid had leaked[14].

f) In 1979, a patient received 50mL of a 5% dextrose solution in normal saline. The infusion was stopped when a 'fungus ball' was observed as a result of a hairline crack in the bottle. An associated survey showed 24% of responding physicians experienced contaminated solutions within an eleven year span. In 17 of 21 reported cases, the glass container was visibly defective, and 11 of 12 cases (where information was available) specified 'hairline cracks' as the cause of the contamination[15].

g) Around 1990, a patient received a glucose-saline infusion contaminated with *aerobacter cloacae* and subsequently died. Inspection of the container showed a long crack in the vial heel, where the crack was opened ~1.9μm. This spacing between crack faces is insufficient to equalize air and vacuum pressure inside and outside the vial, but liquid can transport through capillary action and contaminate the contents[16].

h) In 1996, patients in 2 distant US states developed similar bloodstream infections due to cracked containers from the same drug manufacturing lot. The infections prompted a recall of the affected lots and the corresponding investigation noted that on more than one occasion during the manufacturing process, cracks were introduced to the vials when pallets of filled vials fell during transport by forklifts. At the end of the recall, only 6525 of 17000 affected vials were recovered[4].

i) And in 2010, three of 11 infected neonates died when their parenteral nutrition was prepared from a bottle that contained a crack[5, 17].

The occurrence rate of containers having a crack is likely underrepresented by these incidents for a variety of reasons. These reports are limited to cases where bacteremia or fungemia occurred and the cause was determined to be a crack in a glass container and the case was published. The symptoms associated with bacteremia, fungemia, and sepsis (fever, chills, pain, fast heart rate, mental confusion) coincide with the adverse events associated with many parenteral products, obscuring detection and quantification. Furthermore, the recipients of certain parenteral medications have multiple risk factors for infection because they typically have many medical problems and have undergone multiple invasive procedures, decreasing the likelihood of investigation and identification of a cracked container cause[4]. These events often require multiple affected patients (epidemic) to prompt investigation, further complicating quantification of the frequency. The transition from multi-dose to single-dose packaging[18] should decrease the scale of epidemics from a cracked container, but it would not prevent or reduce the occurrence of isolated cases[11]. In fact, isolated cases caused by single-use containers may go undetected – potentially affecting more patients over a longer period of time. Wang, et al. state that

poor tracking of broadly-distributed medications (and their patients' responses) can mask identification of even systemically-cracked populations (crack occurrences as high as 1.5% within a lot)[4].

The pharmaceutical manufacturing industry has invested significantly in inspection technology, but each year injectable drugs continue to be recalled or investigated by the manufacturer for sterility risks associated with cracks. Optical inspection methods for glass containers rely upon special alignment of the detector, light source, and crack for detection, resulting in significant risk of false negatives. As a result, these methods can often fail to detect cracks effectively. Recently-revised US Pharmacopoeia chapters on package integrity testing[19] describe that classical dye- or microbial- ingress methods are probabilistic and therefore cannot reliably ensure container closure integrity. Online, deterministic techniques are more reliable at detecting lower frequency violations in an objective manner. Yet within the last 5 years, there have been at least 11 recalls due to cracked containers, affecting millions of vials (see Table I).

Considering the increasing use of parenteral medicines[20-22], the seriousness of issues with container integrity failure, the challenges with detecting cracks, and the likely underreporting, it is highly desirable to prevent these failures in an effort to improve patient safety.

Understanding crack formation in conventional glass containers

Brittle materials such as glass are very strong when placed under compression, but can break when placed in tension. The strength of glass under tension is limited in practice by flaws, which are cuts or gaps in the atomic bonds at the glass surface. Applied tension concentrates at the tip of flaws (i.e., checks, scratches, and even cracks), causing flaw extension (propagation) if the concentrated tension exceeds the strength of individual atomic bonds. Figure 2 illustrates the stress concentration at the flaw tip when the sample is experiencing uniform tension. Flaw extension can stop if the applied tension decreases over time, or if the flaw grows into a region of low tension. If the applied tension is sufficiently uniform and outlasts the flaw propagation, the flaw will extend (both through the wall thickness and away from the origin) and the container will break. Cracks occur whenever the stress applied allows the flaw to extend through the wall thickness, but the propagation stops before the container breaks. Cracks occur (and are stable) in conventional glass containers because they contain only minimal residual stresses, driven low by thermal annealing during forming.

The initial surface flaws in glass containers are introduced primarily from contact with other surfaces during forming, transport, filling, and handling. These types of contact are pervasive throughout the conventional glass container manufacture process (regardless of manufacturer) and therefore all glass containers exhibit surface flaws (with significant variation in severity). When these surface flaws subsequently experience applied tension, they may grow into cracks or breaks depending upon the duration of the applied tension and the alignment of the original flaw with the applied tension. As a result, cracks form in certain regions of the vial more frequently than other regions due to the severity and frequency of the original flaws and their alignment with the applied tension.

A survey of failed vials was conducted to determine the most common locations of cracks in borosilicate containers. Type I borosilicate vials returned to pharmaceutical companies due to the presence of

cracks were shared with Corning Incorporated for this study. The returned containers included a wide range of dimensions (3 to 40mL) and both molded and tubular forming methods. Modern fractographic techniques[16] were applied to determine the origin and categorize each crack location. The location categories are illustrated in Figure 3. In total, 81 cracked vials were inspected and the results showed that more than 90% of cracks occur in the heel, footprint, and body regions. The remaining regions (bottom, shoulder, neck, flange, seal surface) experienced cracks much less frequently (<10%).

A separate fractographic survey inspected more than 200 borosilicate vials that were returned to various pharmaceutical companies as part of customer complaints (not necessarily cracked). The inspection categorized sources of breakage, cracks and damage introduced by the pharmaceutical filling lines and in-field handling. This fractographic survey and root cause investigations revealed 3 common modes of container damage leading to breakage and crack formation: bump checks, bottom lensing, and neck cracks.

Bump checks, sometimes called bruises, are typically crescent-shaped surface marks caused by a mechanical bump or glass-to-glass contact. They are classified within PDA Technical Report 43 as either *Minor* or *Major A* defects based on their size because while a minor nonconformity may "not impact product quality or [filling] process capability," a major defect may lead "to serious impairments or malfunction that makes the packaging unusable[10]." Checks by themselves are not classified as *Critical* because they do not yet present a sterility risk, but larger bump checks would be considered *Major A* because they can lead to cracks by subsequent applied tension. This 200 part survey showed that approximately 80% of the customer complaint containers exhibited bump checks in the heel. Given their heel location and high frequency, bump checks are a leading root cause of many cracked containers.

Lensing is defined as a 'glass container bottom that is completely separated from its body' and is classified as a *Critical* defect because it 'compromises the integrity of the container and risks microbiological contamination of a sterile product[10].' The mechanical process that creates lensing also creates bottom lens cracks, where the footprint and heel regions contain a large crack but the bottom does not completely separate. These cracks can be difficult to detect during automated or visual inspection due to the narrow crack opening widths and the three dimensional curvature of the vial heel and footprint. Bottom lens cracks, while they do not occur as frequently as bump checks, are high risk to patient safety due to the difficult detection and large crack paths provide opportunity for vast microbial transport.

Neck cracks were observed less frequently in both surveys (<10% of cracked container field returns) but may occur during capping operations on commercial filling lines and may be very difficult to detect. All cracks are classified as *Critical* defects[10], but neck cracks are especially concerning because they are generally more difficult to detect than cracks in the body due to the three dimensional curvature in this region and the potential masking by the aluminum cap. While there are many mechanisms for introducing neck cracks, several involve misalignment of capping equipment. In one case, the authors observed a fixed crimp seal rail was configured to seal a different geometry than the vial being

processed (i.e., configured for smaller neck diameter). Neck cracks were introduced where the crimping equipment contacted the neck of the vial.

Once they are introduced, cracks in conventional containers will remain stable until another force is applied. For example, if additional tension were applied after a crack were present, the tension could cause the crack to continue growing larger or could cause the container to break. However, without an applied tension (mechanical load, thermal gradient, pressure gradient, etc.), the cracks will persist indefinitely because other drivers to propagate cracks (such as residual stresses[10]) have been relieved or homogenized by thermal annealing during the forming process. If an applied tension of sufficient magnitude and duration were present, cracks would propagate to failure (breakage) rather than present a container integrity risk.

Conventional glass containers are therefore susceptible to forming cracks because (1) they contain initial surface flaws from forming, handling, and transport damage, (2) they experience ample tension during filling and handling that can cause these flaws to grow into cracks, and (3) they have insufficient tension to cause the crack to propagate and lead to breakage. Most cracks are introduced in the body, heel, and footprint regions of a vial as a result of bump checks, while less frequent high-risk cracks (because detection is difficult), such as neck cracks and bottom lensing, are introduced in the neck and footprint.

Three methods for replicating stable cracks in parenteral containers

Fractographic evidence observed during inspection of field returns revealed a variety of ways that cracks are introduced to different regions of borosilicate glass vials, and three common failure modes are explored in more detail here. To demonstrate understanding of the conditions causing failure, controlled lab experiments are conducted to replicate the failure, including its fractographic features. Inclusion of fractographic features in the replication process assures that the stresses present at the moment of fracture within the glass container are also being reproduced. Well-controlled methods can then be applied to evaluate differences in test condition or container design. Here, we demonstrate the ability of these methods to replicate the fractographic features of the three failure modes and later apply the methods to evaluate crack behavior in vials with an engineered stress profile.

A bump check contains unique fractographic features such as frictive transfer of material at the contact site, a crescent-shaped initial crack, and in more severe cases the fracture extends in opposite directions away from the origin along a curved path having a "wing-shaped" appearance. Figure 4 is a photograph of a crack in a field-returned Type I borosilicate vial which originates at a bump check and extends through the glass wall. This example is representative of the typical features of these defects, but not all bump check defects contain all of these features.

Figure 5 shows a schematic of the experimental setup used to replicate this defect: a 3 mL vial placed on a 33° sine plate fixture in a 5 kN load frame. The photograph in Figure 5 shows a 16 mm borosilicate ball positioned to contact the vial sidewall approximately 2.5 mm from the footprint of the vial. A load is applied to the vial heel by vertical displacement of the ball (indicated by the arrow) to a predetermined peak load. During loading, a crack forms in the tested vial which persists after the load is removed. Cracks are consistently produced in the vials tested using this method.

Figure 6 compares optical microscope images of a representative field return bump check defect to a representative defect created by this experimental setup. Both checks contain evidence of frictive material transfer near the conical center of the crack as well as wing-shaped fractures extending from the origin. Differences in features between samples will exist due to differences in loading rate, peak load, and other unique surface characteristics of each specimen. Despite these differences, the figures show replication of the key bump check fractographic features in orientation and scale, indicating that the experimental setup is able to simulate the conditions that lead to bump check failures.

Lensing cracks were replicated via a two-step process: surface damage introduction followed by a dynamic impact (light strike). As illustrated in Figure 7, damage was first introduced to the footprint of 3 mL vials by contact with 90 grit silicon carbide fixed abrasive grinding paper at a controlled normal load of 10 N. Second, the vial bottom center is lightly struck with a low pressure pneumatic actuator putting the footprint in tension and propagating the initial damage to a lensing crack.

Figure 8 compares the fractographic features of a lens crack from a field return with those generated by this method. The field return sample (Figure 8a) shows the crack propagating for about half of the circumference, before stopping in the heel or lower sidewall. These cracks are particularly difficult to detect due to the narrow crack opening widths (preventing light reflection from its features) and the three dimensional curvature of the heel and footprint region. The microscope images (Figure 8b) show features of the lens cracks produced with this method. The photos (at higher magnification than 8a) show the part of the crack system in the heel where the fracture terminates because the stress was removed.

Neck cracks can be introduced by interactions with capping equipment. This defect was previously observed in borosilicate vials capped by several methods, including rotating the vial against a static sealing rail system and by free-spinning displacement-driven crimping wheels. Since the introduction of these crack systems is difficult to control, the container response for defects in this region was evaluated using a rotary disc (low speed diamond blade). Figure 9 illustrates how the rotary disc was used to damage the neck of a vial in a similar location to that of a misadjusted automatic crimping wheel. This method more consistently introduced severe damage in the vial neck and manual inspection provided observations of differences in container response. The response of the vial to this type of insult can be categorized as either cracked (if the disc induces damage completely through the neck and the vial remains intact), or broken (if the vial flange separates from the neck before the disc induces damage completely through the neck).

Dye ingress leak testing

Dye ingress leak testing was employed to confirm that perceived cracks (identified by human inspection) generated in the replication experiments completely penetrated the glass container and presented patient safety risk. Following the recommendations in USP<1207.2>, a procedure was developed where vials were filled to a nominal volume with high purity water, stoppered, and sealed[23]. The sealed vials were submerged in a 0.1% methylene blue dye solution and vacuum of -85 kPa was applied for 60 minutes. During this time, the pressure differential created by the vacuum could draw gas or fluid out of

the vial through cracks. The submerged vial system was then vented to ambient pressure for 60 minutes, allowing the dye solution to be drawn into vials which had previously leaked gas or liquid during the vacuum step. Considering the low pressure used in this method, it is unlikely that significant flaw extension occurs from the applied pressure. Vials were removed from the solution, rinsed thoroughly, and manually inspected to determine if dye ingress occurred.

As recommended by USP<1207.2>, reference solutions and negative controls were implemented to ensure consistency of results. Reference solutions were created by 11 serial dilutions of the 0.1% methylene blue solution between 0.05% and 0.000049% for semi-quantitative inspection. The test specimens were compared to these references and a process blank against a white background as shown in Figure 10. Negative controls were created using as-received (non-damaged) vials that were filled, stoppered, and crimp sealed under identical conditions and vacuum tested alongside each sample set to ensure any identified leaking vials were not a result of the crimping procedure. Any leaking of these negative controls during testing would have indicated poor sealing of the glass flange, rubber stopper, and aluminum cap closure system. No failures of the negative controls were observed in any of the test sets.

Preventing formation of stable cracks

Cracks in glass parenteral containers present a serious risk to patient safety (ineffective dose, lack of sterility, contamination leading to sepsis or even death) and to the drug supply chain stability (recalls and resulting shortages), and should therefore be prevented. It is well-known in other glass applications that strengthening techniques can inhibit flaw introduction and growth and also control the fracture behavior when glass does break (number of fragments, their shapes, etc.). For example, thermally-tempered safety glass used in automobile and architectural applications is engineered to have a region of compressive stress at the surface that hinders damage introduction and flaw extension. In addition, when safety glass does break (at higher load than non-tempered glass) the fracture propagates to the extent of the tempered region and produces small, harmless, approximately cubic-shaped fragments to prevent injury from 'dagger-like' fragmentation typical of annealed glasses[24].

Not all strengthening processes are able to impart special fracture behavior. Processes producing lower levels of strengthening (less stored strain energy) may exhibit strength improvements over non-strengthened glass but with the same 'dagger-like' fragmentation pattern as annealed glass[24]. Special fracture behavior is only enabled when the strengthening process produces sufficient strain energy to influence the flaw propagation[25]. Lawn and Marshall describe that for samples with sufficient internal tension, a crack will tend to propagate catastrophically once it penetrates the protective surface layer[26]. This means that flaw tips which remain within the compressive surface layer will remain benign; and flaws which penetrate into the tensile region (at the center of the wall thickness) can propagate under the stored strain energy. A similar strengthening method can be applied to glass containers for pharmaceutical applications to prevent formation of stable cracks.

Ion-exchange strengthening (or chemical tempering) is another method that can impart this threshold strain energy. It is better suited to strengthen thin walls, glass compositions with low thermal expansion

coefficient, and complex container geometries compared to thermal tempering[27]. The process uses chemical gradients and interdiffusion to substitute larger ions from an external salt bath for smaller ions in the glass network. This substitution creates a compressive stress on the surface of the container and a balancing central tension over the thickness of the container wall as illustrated in Figure 11. Because the stress profile is the result of interdiffusion, exposure time and temperature can be controlled and monitored during the manufacture of the glass containers to maintain the strain energy (or central tension) above the minimum tension threshold value for crack prevention.

An aluminosilicate glass, previously shown to be suitable for pharmaceutical use[28], was strengthened by the ion-exchange process as part of this study. A series of glass vials was prepared with increasing levels of central tension (or stored strain energy) by varying the ion-exchange process (time and temperature) to explore changes in the material's fracture response. The containers were then subjected to controlled damage to observe the fracture response. Figure 12 illustrates the decrease in frequency of cracked vials produced as a function of increasing central tension (as surrogate for stored strain energy). The graph shows a clear 'threshold' response, above which damage suitable to produce cracks in unstressed vials causes obvious breakage patterns (stable cracks are not maintained).

Demonstrating prevention of stable cracks

To demonstrate the prevention of stable cracks with the strengthened aluminosilicate vial, several methods were employed: i) replication of common crack failure modes using lab tests, ii) statistical analysis and interpretation of the lab results, iii) a line simulation with a misadjusted capper to assess performance using actual pharmaceutical processing equipment, and iv) evaluation of automatic visual inspection system in use on pharmaceutical filling lines to assess prevention of cracks relative to the current state-of-the art processing equipment used for this purpose.

Lab Replication of Common Failure Modes
Differences in vial cracking response were illustrated by applying the crack replication methods to typical borosilicate and ion-exchange strengthened aluminosilicates vials. Glass vials of equivalent dimensions (3 mL nominal fill volume) were formed from tubes of two glass compositions (51-expansion borosilicate, and strengthened aluminosilicate). After forming and annealing, the aluminosilicate glass vials were ion-exchanged to establish the internal stored strain energy above the minimum tension threshold. The strengthened aluminosilicate glass vials received a low coefficient of friction surface treatment which resists glass damage and reduces particle formation[29]. The borosilicate vials underwent typical annealing and bulk packaging. Both populations of vials were then tested via the three high risk crack replication methods described previously followed by dye ingress testing to confirm leaking cracks.

The bump check crack replication method was repeated on 100 typical borosilicate vials and 100 strengthened aluminosilicate glass vials, then all vials were subjected to the dye ingress leak testing protocol described previously. The borosilicate vial population exhibited perceived cracks (by human visual inspection) with 100% of the population tested. Dye ingress testing confirmed that 20 vials leaked

(20%), as summarized in Table II. The strengthened aluminosilicate glass vials showed no perceived cracks and no leaking upon dye ingress testing.

The bump check crack introduction method was then increased in a stepwise manner to test if cracks could be introduced in the strengthened aluminosilicate glass vials. Despite increasing the load by 35%, the tests showed no observation of cracks, instead the vials began to break - consistent with the bimodal response expected.

The absence of cracks in the aluminosilicate vials under the same conditions that consistently cracked the borosilicate vials demonstrates a significant difference in crack introduction behavior. The load needed to observe cracks will be just below that needed to break the container. The absence of cracks and onset of breaking at higher loads indicates that flaws were introduced that exceeded the aluminosilicate compressive layer depth. The binary response of the aluminosilicate vials (intact or broken) is expected because the stored strain energy was above the threshold shown in Figure 12.

The lensing crack replication method was performed on 50 typical borosilicate and 50 strengthened aluminosilicate glass vials. After going through this damage replication process, manual inspection confirmed that all conventional borosilicate vials contained perceived cracks. Aluminosilicate vials that had been through the same crack replication method showed no signs of damage and zero perceived cracks by manual inspection. Dye ingress testing confirmed that a large fraction (70%) of the cracked borosilicate vials leaked and none of the aluminosilicate vials exhibited leaks.

In parallel, the crack replication conditions (load applied during initial damage introduction and peak load during dynamic impact) were increased to observe a change in the aluminosilicate fracture behavior. After increasing the dynamic impact peak load by 60%, the aluminosilicate vials began to exhibit breaks. For the engineered stress profile imparted to these aluminosilicate vials, cracks were not created for any combination of initial damage introduction or dynamic impact conditions. When damage was introduced that penetrates deeper than the compressive layer, the stored strain energy serves to extend the flaw, propagating to cause breakage and make the damage obvious.

An evaluation of the container response to severe neck cracks was performed on a smaller population of 20 vials per glass type. The method was designed to demonstrate the inherent nature of crack stability in conventional glass vials and illustrate the release of stored strain energy via fracture with the strengthened aluminosilicate vials. Figure 13 compares representative micrographs of a conventional vial to a strengthened aluminosilicate vial after damage from a rotary disc, showing different fractographic responses. For the conventional borosilicate vial, the rotary disc completely penetrates through the vial neck with no fracture observed, only a roughened cut surface from the disc. This means that the rotary disc carved a large pathway through the neck thickness (an exaggerated crack) of the conventional borosilicate vial without the flange separating from the neck. For the strengthened aluminosilicate vial, the image shows that the rotary disc penetrates less than 75% through the thickness of the neck before the stored strain energy (central tension) caused the glass to fracture and the flange to separate from the neck.

These results illustrate that strengthened aluminosilicate glass vials show a marked differentiation in fracture behavior, exhibiting no cracks in any of the tests and no detection issues during automated inspection.

Statistical Analysis of Lab Replication Results

A statistical analysis was performed to quantitatively compare the probability of failure of these two vial types (borosilicate or aluminosilicate) for the two probabilistic damage replication methods (bump check and lensing crack). The binomial distribution was used, in which case the median probability of the failure mode occurring was calculated, i.e. the probability for which the cumulative binomial probability is 0.5. Additionally, the 80% two-sided and 95% two-sided confidence bounds around these median values were determined by calculating the failure rate for which the cumulative binomial probability is 0.1 and 0.9 (for the 80% level) and 0.025 and 0.975 (for the 95% level).

Since the tests of aluminosilicate vials did not produce any failures, the calculated probability values only represent an upper bound. For example, in the lensing crack replication method, there were 50 aluminosilicate samples tested with no failures. As such, there is 97.5% confidence that the true probability of occurrence is less than 0.071, and a 90% confidence it is less than 0.045.

The tabulated results for producing leaking cracked vials are shown in Table III. The results show that differences between the borosilicate and aluminosilicate failure probabilities are significant (evident by the separation in the confidence bounds). Differences in median values are greatest for bump check and lensing crack replication methods, where borosilicates are at least 30 to 50 times more likely to exhibit leaking cracks.

Since the rotary disc cut demonstrated a targeted response with the binary result of cracked or broken, the predicted results of a statistical analysis is only subject to the number of specimens tested and more insight can be gained from the fracture response than probabilities. As described previously, the fractographic response of the conventional borosilicate vial is to allow the disc to cut completely through the neck thickness and in contrast, the strengthened aluminosilicate vial will tolerate the disc cutting only up to 75% of the neck thickness before the vial breaks. This demonstration of the response due to stored elastic strain energy is physics based and not probability based.

It was previously noted that 90% of cracks observed in failed vials occurred in regions of the vial evaluated by these crack replication methods (~80% - bump checks, <10% - lensing cracks). Assuming that these replication methods are representative of actual stresses incurred on filling lines and in the field, we can apply the relative frequency of occurrence to estimate a cumulative probability of crack occurrence in each vial type. The total median failure probabilities for leak introduction in each glass, weighted by these percentages, are for borosilicate - 0.200 and for aluminosilicate – less than 0.0064. This implies that for ~90% of cracked containers, conventional glass is more than 31 times more likely to fail due to leaks than aluminosilicate, essentially preventing cracks in the strengthened aluminosilicate containers. Given the physics-based understanding of the fracture response, this scale factor (31 times) is smaller than what larger populations are expected to show, due to the small sample sizes used in this study.

Line Simulation with Misadjusted Capper Equipment

A mixed population of 400 typical borosilicate and 200 strengthened aluminosilicate glass vials were processed through a misadjusted capper (most vials exhibiting some damage) resulting in 13 perceived cracks and 1 breakage in the typical borosilicate vial population and 0 perceived cracks and 8 breakages in the strengthened aluminosilicate glass vial population. Dye ingress testing confirmed that 2 of the 13 perceived cracks in typical borosilicate vials were leaking and 0 of the strengthened aluminosilicate glass vials were leaking as summarized in Table IV.

These results show that the damage introduced by the misaligned capping equipment was severe enough to crack and break borosilicate vials and cause breakage of several aluminosilicate containers. The experiment further illustrates the binary response (intact or broken, not cracked) for the aluminosilicate containers. Further, the engineered stress profile makes damage introduced by filling lines more evident so that operators can immediately address setup issues and prevent creation of systemic cracks.

Evaluation of Automated Visual Inspection System (current state-of-the-art)

A leading automated visual inspection was used to evaluate the efficiency of current state-of-the-art systems to reliably detect cracks relative to the strengthened aluminosilicate vial, which was designed to prevent cracks.

The lensing crack replication method was performed on 50 conventional borosilicate and 50 strengthened aluminosilicate glass vials. After experiencing this damage replication process, manual inspection confirmed that all conventional borosilicate vials contained perceived cracks. Aluminosilicate vials that had been through the same crack replication method showed no signs of damage and zero perceived cracks by manual inspection.

All vials were inspected by an automated camera system to evaluate the capability of the inspection equipment to detect cracks in the footprint and heel areas. The commercially-available camera system was specifically designed to identify cracks in this region of the vial with the camera orientation illustrated in Figure 14a. Table V quantifies the results and shows that the automated camera system captured 74% of the containers with known cracks and failed to detect 26% of the cracked vials processed through the system. Dye ingress testing was performed and identified that 70% of all of the lensing replication borosilicate vials were leaking, including 35% of the cracks that had been accepted by the visual inspection (Figure 14b). This shows that even the best automated visual inspection system, performing 100% inspection, is unable to reliably detect cracks that present sterility risks.

In contrast, none of the strengthened aluminosilicate glass vials showed evidence of damage or perceived cracks, despite having been subjected to the same damage process. Automated inspection did not reject any of the aluminosilicate vials and dye ingress testing demonstrated that none of that population exhibited leaking cracks.

The reduction in crack occurrence demonstrates that stable cracks are essentially prevented when glass vials are strengthened to levels above the minimum tension threshold. While automated inspection can detect some cracks that are introduced during the filling line process, it does not protect against crack

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occurrence after the filling process from prior or new damage events. The stored strain energy that prevents cracks in the aluminosilicate containers persists through handling, transport, and end use at the patient.

Engineered safety benefits of glass in other industries

Engineering safety into glass product design is not a novel concept. As mentioned earlier, automotive and architectural glasses are designed to reduce harm in the event of glass breakage[24]. Automotive glass uses lamination and thermal tempering to increase the safety of passengers in the event of a collision. The lamination prevents glass fragment ejection and prevents passenger ejection during a collision[30]. Automotive side and rear windows are made of thermally-tempered glass which has high stored strain energy in the glass. This stored strain energy aids in egress of passengers from an overturned vehicle by causing the window to fracture into many small pieces after being struck with an emergency hammer.

Architectural glass is also thermally tempered. If an overstressing situation occurs, the thermal tempering also causes the window to fragment or dice into small squared-off pieces of low mass which minimize harm in overhead applications. Both laminated and tempered glass for automotive and architectural use are subjected to strict testing standards to ensure manufactured product performs as expected during use. Their reliability has been demonstrated and now federal regulations require their use in many applications like shower doors. This approach of engineering safety into product design and manufacturing through standards setting can also be applied to pharmaceutical glass packaging to prevent harm from cracked glass containers.

Conclusions

Glass is the preferred primary packaging material for parenteral drug products, but the risk of cracks in conventional glass containers cannot be mitigated through inspection alone. The low energy state of conventional glass vials allows crack systems to persist indefinitely, presenting opportunities for sterility loss and patient harm if the compromised dose is administered. Introduction of stored strain energy was shown to provide sufficient driving force to prevent stable cracks in vials made from an aluminosilicate glass.

Three crack failure modes were identified in various field return surveys and replicated in controlled laboratory damage introduction methods. Differences in cracking behavior were observed when these methods were applied to both conventional borosilicate and strengthened aluminosilicate glass vials. Specifically, the conventional glass vials exhibited cracks with high frequency and were not detected reliably by state-of-the-art automated inspection equipment. Strengthened aluminosilicate glass vials did not exhibit cracks under any of the testing methods. In one instance (neck cracks from line simulation with misadjusted capper equipment), the strengthened aluminosilicate glass vials broke in obvious ways to signal a setup issue, while the borosilicate glass vials sustained a high frequency of stable cracks that were difficult to detect with visual inspection.

These crack failure modes observed in conventional glass containers can be prevented through stored strain energy as imparted through an ion-exchange process. By utilizing glass with sufficiently high stored strain energy, containers for pharmaceutical packaging can follow the automotive and architectural industries to design for improved patient safety.

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Conflict of Interest Statement:

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Figures:

Figure 1: Cracked borosilicate vial of contaminated human albumin which upon injection resulted in blood stream infections for patients[4].
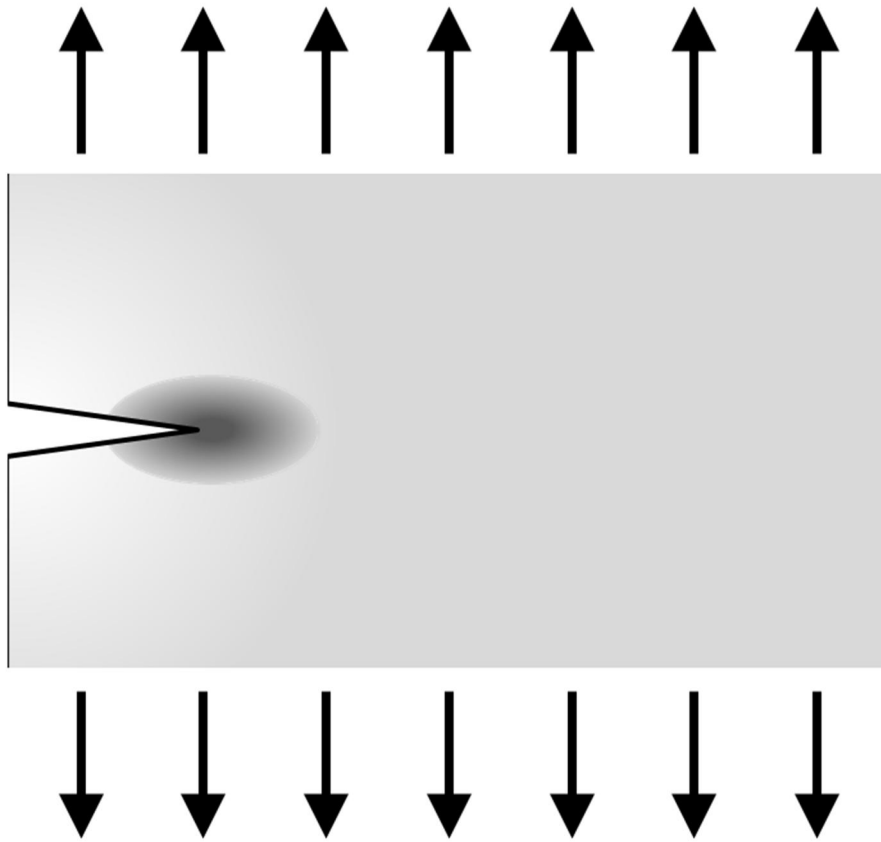
Figure 2: Cross-sectional schematic of a glass article under uniform applied tension, showing low level stress (grey shading) throughout the part and high stress concentration (dark grey shading) near the flaw tip.
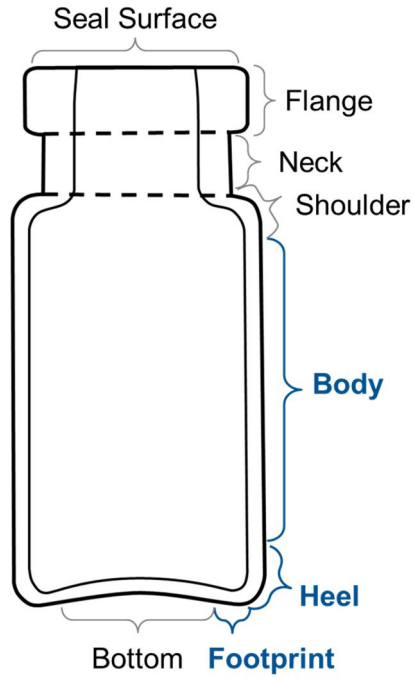
Figure 3: Vial schematic labeled with common locations. The highlighted regions (Body, Heel, & Footprint) show where more than 90% of cracks are introduced.
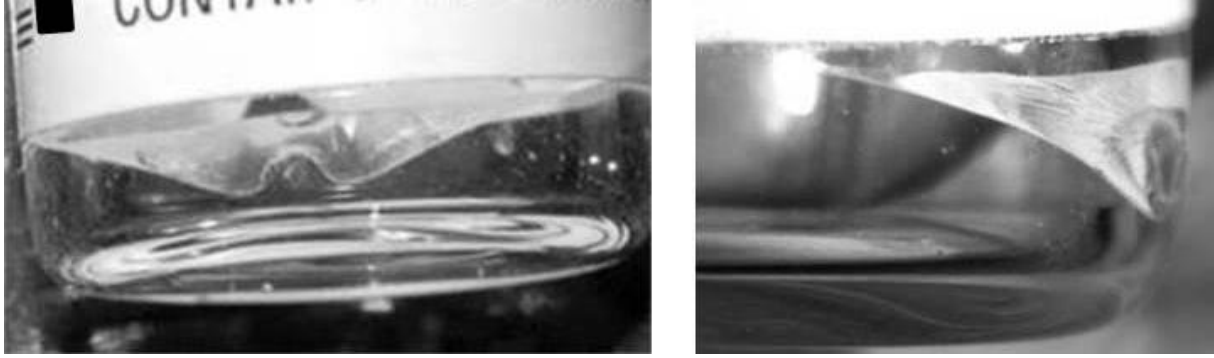
Figure 4: Photograph of a borosilicate vial returned from the field with a bump check crack that extends through the glass wall that was formed during shipping to the health care facility.
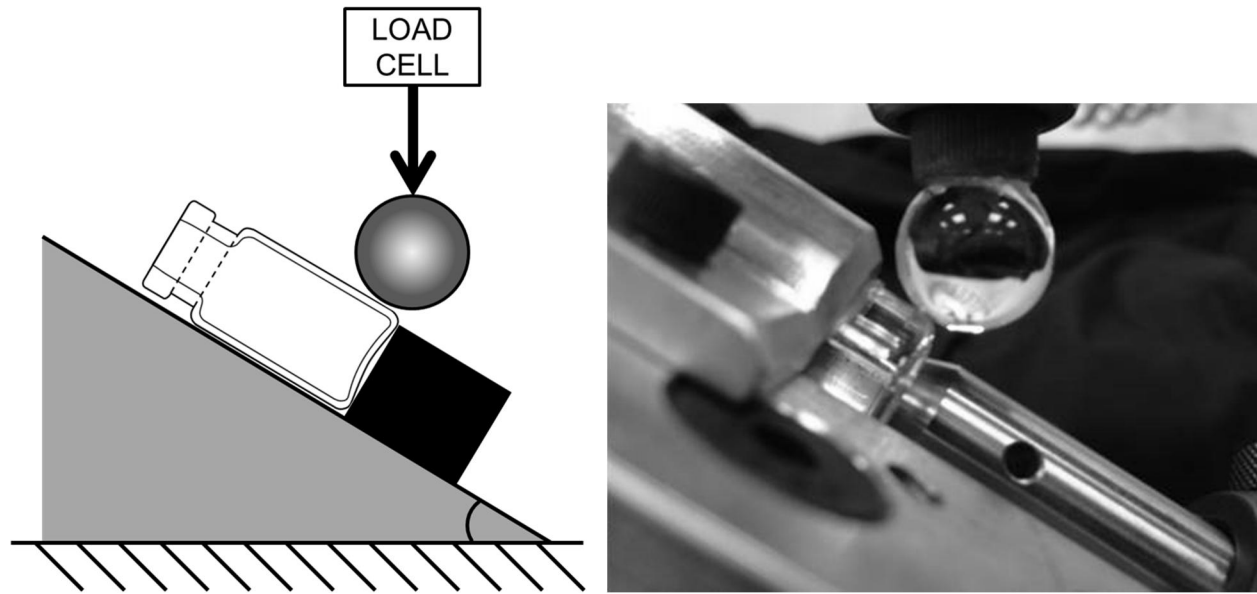
Figure 5: Mechanical testing equipment designed to replicate the features of a bump check crack by loading a vial heel with a sacrificial borosilicate glass ball.

Field return vial
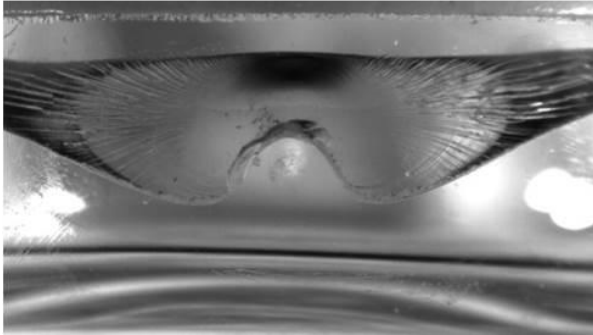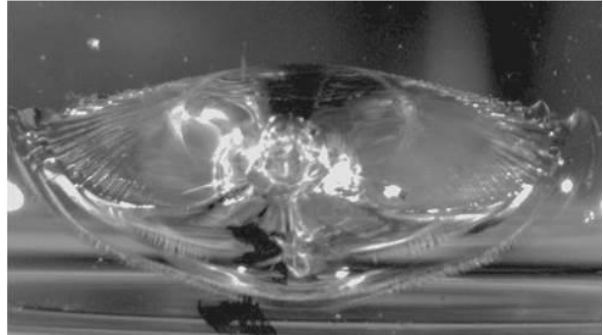
Laboratory replication borosilicate vial

Figure 6: Optical microscopy comparison between a field return bump check crack and the laboratory replication, showing key fractographic features: frictive material transfer, crescent-shaped initial crack, and fracture propagating away from the origin creating "wing-shaped" features. The replication of these features demonstrates that the mechanical testing equipment is able to generate bump check cracks in borosilicate vials.
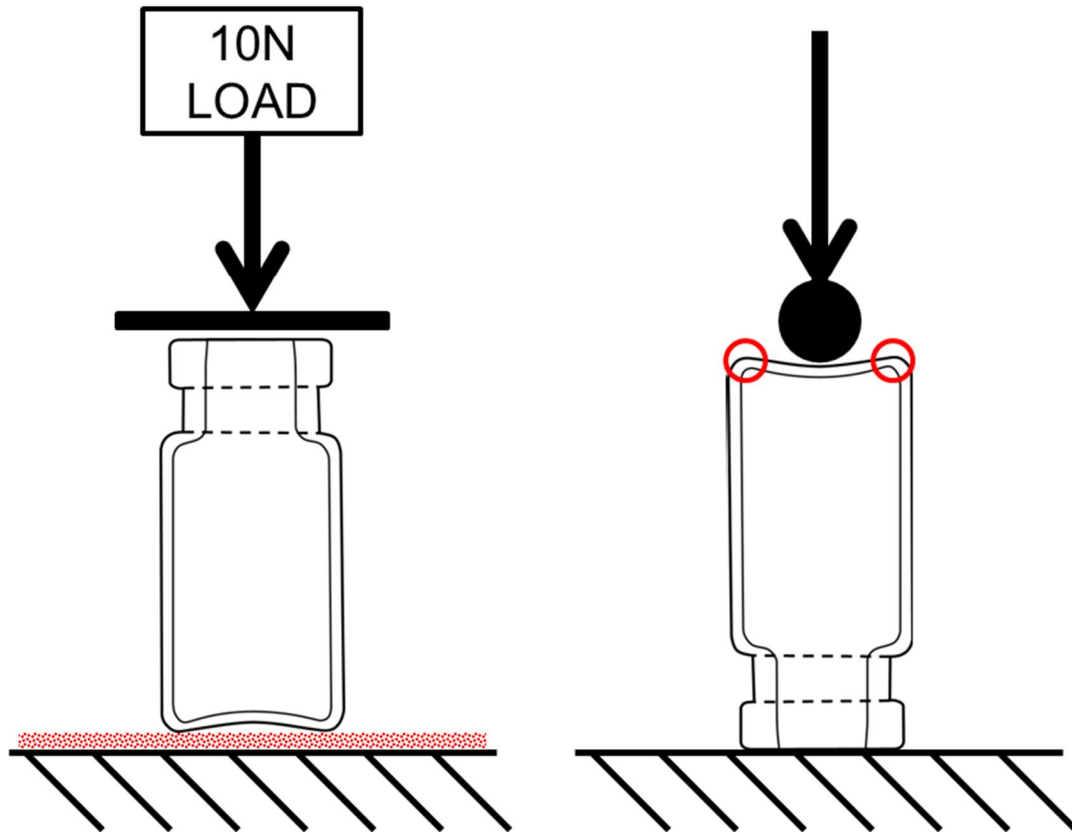
Figure 7: Schematic of two-step process of creating lens cracks. At left, the borosilicate glass vial is pressed into silicon carbide fixed abrasive paper (textured surface contacting vial footprint) with a 10N load, creating initial surface damage in the footprint region. At right, the center bottom is then lightly struck with a low pressure pneumatic actuator putting the footprint in tension and propagating the initial damage to a lensing crack.
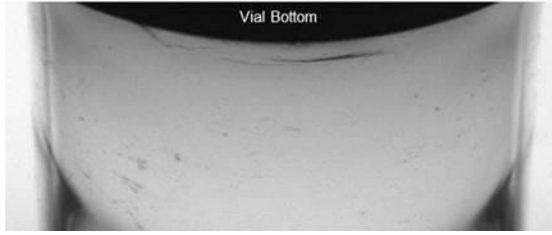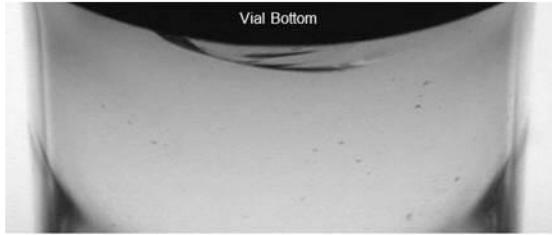
Figure 8: a) Field returned borosilicate vials that experienced a lensing crack that propagated up the sidewall from additional applied stress but did not break the vial. b) Optical microscopy image of two vials from controlled lab experiments that replicated these lensing cracks.
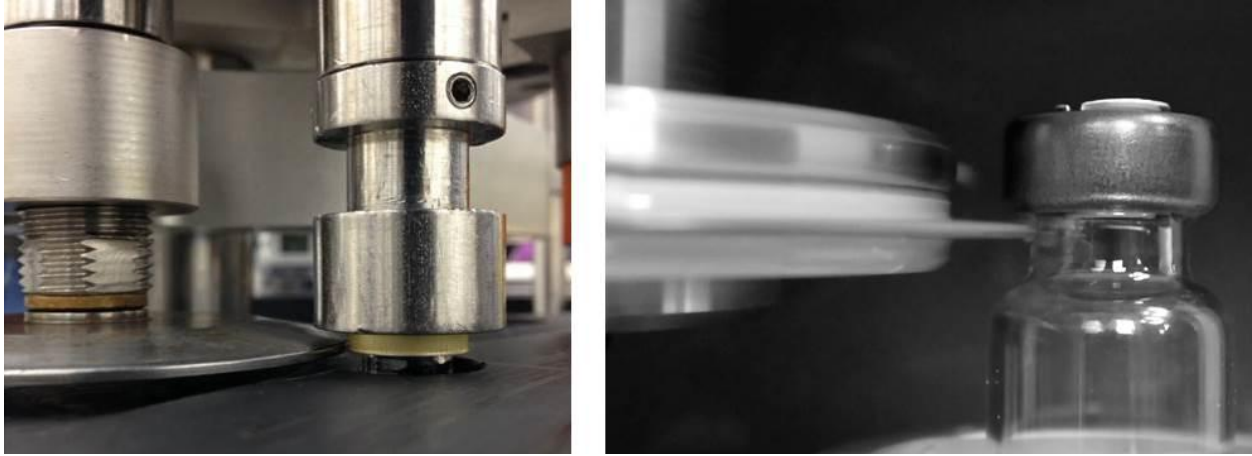
Figure 9: a) At left, seal crimping equipment configured to shape aluminum caps on vials. When operating, the crimping wheel (at lower left of image) is displaced a fixed distance toward the neck OD (at lower right), bending the aluminum cap under the flange. The vial being processed has larger neck OD, causing the crimping wheel to damage the glass surface in the vial neck. b) At right, rotary disc blade cutting into vial neck mimicking the location of damage from seal crimping equipment contact. Cutting through the vial neck with the rotary disc without the vial breaking demonstrates the stable nature of cracks in conventional glass vials. However, if the vial breaks before the disc can completely penetrate through the neck, that vial is not at risk to cause patient harm through the injection of contaminated drug product.

Figure 10: Positive control population for semi-quantitative comparison of dye ingress tests. The vial set shows (from left to right) a process blank (no methylene blue) and serial dilutions of methylene blue dye from 0.000049% to 0.1%.
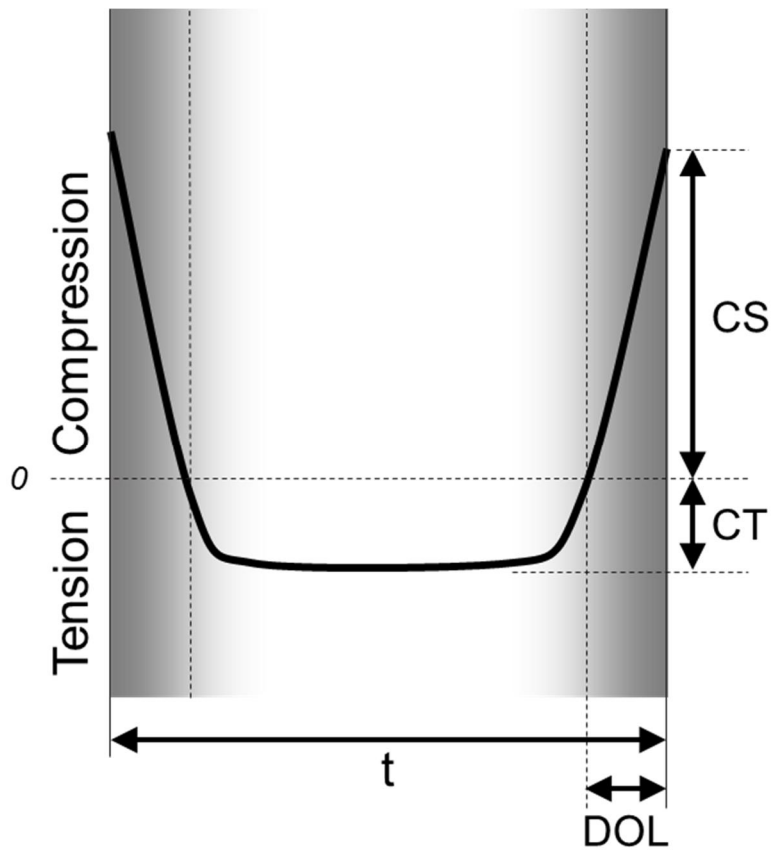
Figure 11: Illustration of the engineered stress profile resulting from ion-exchange of a thin-walled glass article, where the abscissa is the wall thickness (t, radial direction) and stress is the ordinate.   High compressive stress (CS) is installed at the surfaces and it decreases to the depth of the compressive stress layer (DOL). The compressive strain energy induced by this ion-exchange process is balanced by tensile strain energy, measurable as central tension (CT).
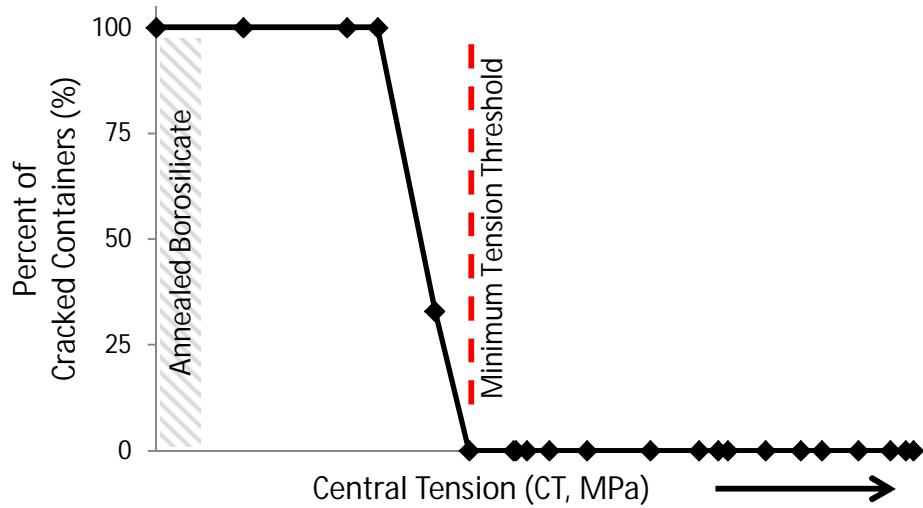
Figure 12: Percent of containers exhibiting stable cracks from damage introduction, as a function of increasing central tension. The response shows a clear 'threshold' response, above which damage (severe enough to cause cracks) causes obvious breaking into fewer pieces with clean edges, facilitating detection.
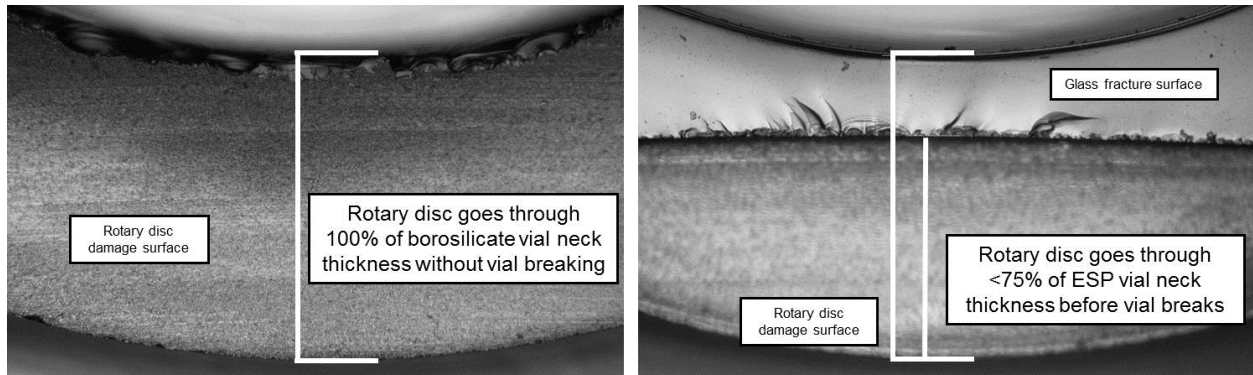
Figure 13: a) At left, an image of a conventional borosilicate vial neck showing rotary disc damage going through the neck thickness without flange separating from the neck. b) At right, an image of a strengthened aluminosilicate vial neck after a rotary disc damage demonstrating that the disc penetrated less than 75% of the way through the thickness before central tension from the engineered stress profile (ESP) initiated the glass fracture and separated the flange from the neck. This response prevents the vial from being at-risk of containing a contaminated drug product that could be administered to a patient.

Figure 14: a) At left, an illustration shows the orientation of a state-of-the-art automated inspection camera designed to reject vials with cracks in the lensing crack region, with an example photo at bottom. b) At right, a photo of vials that were accepted as good by the automated inspection system shows that they clearly failed the dye ingress testing as indicated by the presence of blue dye.

Table I: Eleven recalls issued for injectable pharmaceuticals within the last 5 years due to a lack of sterility associated with cracked glass containers.

Drug	Date	Company	Country	Source	Recall Number
Yervoy	10/18/2014	Bristol-Myers Squibb	Canada	http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/41861a-eng.php	*
Amoxil	10/15/2014	GSK	UK	https://www.gov.uk/drug-device-alerts/drug-alert-amoxil-vials-for-injection-500mg-and-1g-augmentin-intravenous-600mg-and-1-2g-cracks-in-vials-used-for-packaging	*
Methotrexate Sodium	12/18/2013	Teva	Canada	http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/37319a-eng.php	*
Oncaspar	11/15/2013	Link Medical Products Pty Ltd	Australia	http://apps.tga.gov.au/PROD/SARA/arn-detail.aspx?k=RC-2013-RN-01226-1	RC-2013-RN-01226-1
Pegaspargase Oncaspar	11/1/2013	Sigma-Tau Pharmaceuticals	USA	http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm	D-736-2014
Recombivax HB	6/26/2013	Merck	USA	http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm359493.htm	B-0625-14
Cefazolin	5/30/2013	Sandoz	USA	http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm	D-597-2013
Vancomycin Hydrochloride	2/7/2013	Pharmaceutical Partners of Canada	Canada	http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/23809r-eng.php	*
Cyanocobalamin	9/27/2012	Fresenius Kabi	USA	http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm	D-0297-2015
Cyanocobalamin Injection	4/2/2012	American Regent	USA	http://www.fda.gov/Safety/Recalls/ucm298545.htm	*
Midazolam / Heparin / Ketorolac Tromethamine / Ondansetron / Diazepam	7/8/2011	Hospira	USA	http://www.fda.gov/Safety/Recalls/EnforcementReports/ucm282859.htm	*

Table II: Results of dye ingress testing for borosilicate and strengthened aluminosilicate vials after experiencing bump check damage replication. No leaking cracks were observed for the aluminosilicate vials strengthened with an engineered stress profile, while 20% of the borosilicate vials experienced leaking cracks under the same conditions.

Glass Type	Dye Ingress Testing	
	Quantity Tested	Percent Leaking
Borosilicate	100	20 %
Strengthened Aluminosilicate	100	0 %

Table III: Statistical analysis of the probability of producing a leaking crack in aluminosilicate and conventional borosilicate vials for bump check and lensing crack replication methods, based upon values in Tables II & V. Both 80% and 95% two-sided confidence intervals are calculated, though the intervals reported for the aluminosilicate vials represent upper bounds due to the absence of failures.

Method	Glass	95% two-sided				
			80% two-sided			
				Median		
		0.0250	0.1000	0.5000	0.9000	0.9750
Bump Check	borosilicate	0.1349	0.1577	0.2060	0.2607	0.2918
	aluminosilicate	<0.0003	<0.0011	<0.0069	<0.0228	<0.0362
Lensing Crack	borosilicate	0.5751	0.6228	0.7086	0.7854	0.8214
	aluminosilicate	<0.0005	<0.0021	<0.0138	<0.0450	<0.0711

Table IV: Inspection and dye ingress testing results for vials processed with misaligned capping machine, replicating neck crack damage introduction. Human inspection identified 13 (3.25%) borosilicate vials which contained neck cracks, while no (0%) strengthened aluminosilicate vials were identified as cracked. Leak testing of these vials showed that two (0.5%) of borosilicate vials exhibited leaking cracks and none (0%) of the strengthened aluminosilicate vials leaked.

Glass Type	Vial quantity processed by capping machine	Human Inspection	Dye Ingress Testing
		Percent Cracked	Percent Leaking
Borosilicate	400	3.25%	0.5%
Strengthened Aluminosilicate	200	0%	0%

Table V: Automated inspection and dye ingress testing results for vials that had experienced lensing crack replication damage. The automated inspection rejected 74% of the damaged borosilicate vials, 88% of which leaked in dye ingress testing. Of the 26% damaged borosilicate vials that were accepted, 35% of them leaked in dye ingress testing. While the strengthened aluminosilicate population experienced the same damage replication event, 100% of the vials were accepted by the automated inspection equipment and none of the vials leaked.

Glass Type	Automated Inspection Results	Dye Ingress Testing	
		Quantity Tested	Percent Leaking
Borosilicate	26% Accepted	17	35 %
	74% Rejected	33	88 %
Strengthened Aluminosilicate	100% Accepted	50	0 %
	0% Rejected	0	0 %

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