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Corning Valor® Vials Demonstrate Superior Performance by Resisting Breakage During Low Temperature Processing

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Glass vial failures, specifically breakage, lensing, and cracks, are a source of product loss and process cost in the freeze-thaw, cryogenic preservation, and lyophilization of pharmaceutical products. Lyophilization is a common method for the preparation of freeze-dried pharmaceutical products, which requires low temperature processing to avoid product damage or decomposition.[1] Because process times are long and lyophilization is regarded as an expensive process, considerable research has focused on improving lyophilization rates to reduce costs.[2,3] One contributing factor to cost is the failure of glass vials during the lyophilization cycle, which includes freezing, annealing, and drying process steps. Vial damage or breakage results from elastic stresses generated by the sudden volume expansion of the freezing solutions and crystalline phase changes of solids exceeding the flaw limited strength of the container. This vial breakage results in higher process costs, delays due to destruction of product, and lead to possible drug shortages. Corning Valor® Glass, specifically designed to meet the needs of the pharmaceutical industry, dramatically reduces breakage and enables lower cost lyophilization compared to conventional borosilicate glass vials.

MANUFACTURING ISSUES STEM FROM MATERIAL LIMITATIONS

Glass is the ideal material for parenteral packaging because of its chemical durability, hermeticity, strength, cleanliness, and transparency.[4] Glass is inherently strong; however, the practical strength is influenced greatly by the flaws in the glass. Conventional glass vials are highly susceptible to exterior damage or flaws during the converting process, transit, and on pharmaceutical manufacturing lines.[5] Furthermore, in the lyophilization process, glass is subjected to high hoop stress.[6] Breakage typically results from stress applied during the process exceeding the flaw limited strength in the glass vial and tensile stress. Economically speaking, vial breakage during production of an expensive drug *e.g., an antibody* can be costly since it decreases the yield and effective batch-size, extends the clean-in-place *CIP* procedure during line stoppage, and wastes drug resources.[7,8]

Conventional borosilicate glasses have been used for a long time, but they are prone to strength limiting flaws that can create breakage in the lyophilization process, potentially leading to overall yield reduction due to line stoppage, increased cleaning times, and loss of product. For these reasons, the industry is turning to glass packaging specifically designed for pharmaceutical manufacturing to maximize strength and minimize breakage. One solution is Valor® Glass, an advanced container which maintains high strength from state-of-the-art converting and chemical strengthening. The container is engineered to minimize breakage and retains its strength with a protective, externally applied, damage-resistant, low coefficient of friction coating.

BREAKAGE OF CONVENTIONAL VIALS IS DUE TO STRESS DURING LYOPHILIZATION

Breakage of conventional borosilicate vials is common during lyophilization due to the stresses generated in the glass during the low temperature process exceeding the strength of the vial.[6] Expansion of the freezing liquids and crystalline phase changes of the frozen solids are the two most common sources of stresses causing vial breakage. The stress developed during the expansion of a freezing liquid is applied to the sidewall and bottom of the vial and is a function of the fill volume and drug composition. One example of this can be found with mannitol. This common excipient has a relatively large expansion during freezing and undergoes a crystalline phase change during annealing or drying, adding additional stress to the vial.[9]

FIGURE 1

LENSING FAILURE FROM LYOPHILIZATION OF MANNITOL *BOROSILICATE GLASS*

Jiang. G.; et all. (2007) USA. Figure 9: Typical vial breakage pattern during freeze-thaw of mannitol solution. PDA J. Pharm. Sci. Tech. digital image

FIGURE 2

LENSING FAILURE DURING AGGRESSIVE LYOPHILIZATION LABORATORY CYCLE STUDY *BOROSILICATE GLASS*

Pharmaceutical Manufacturer (photographer unknown). (2018). USA. Aggressive lyophilization cycle lensed bottom, digital image

FIGURE 3

CRACKING FAILURE FROM AGGRESSIVE LYOPHILIZATION LABORATORY STUDY *BOROSILICATE GLASS*

Pharmaceutical Manufacturer (photographer unknown). (2018). USA. Aggressive lyophilization cycle sidewall breakage. digital image

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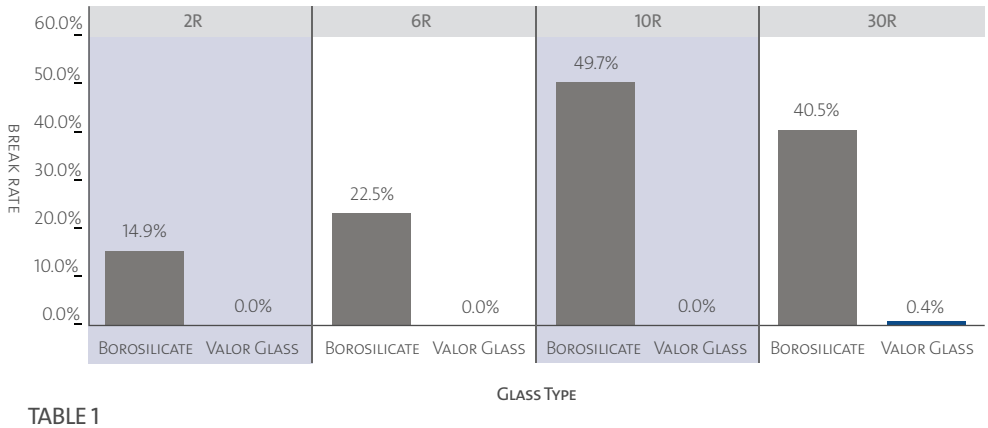

LABORATORY FREEZE-THAW TESTING OF BREAKAGE RESISTANCE USING MANNITOL

One method to evaluate vial breakage problems in lyophilization is freeze-thaw testing. The aggressive test method employed by Jiang et al. was utilized for this study in which vials are very rapidly cooled-down from room temperature to -100°C in approximately 1 minute followed by an uncontrolled thaw from -100°C to room temperature *~12 hours*. All vials contained a 15% mannitol solution at 50% fill volume.[10] To show differentiation in container performance, four ISO vial sizes *2R, 6R, 10R and 30R* of both conventional borosilicate and Valor® Glass spanning a range of diameters *16 mm – 30 mm* and wall thicknesses *1 mm – 1.2 mm* were compared. For statistical representation, 1,000 vials of each vial type and format were utilized.

Visual inspection was performed at the end of the cycle when the vials were back to room temperature to capture the total breakage failure rate. As described by Jiang, vial breakage has been identified in both the freezing as well as the thawing of the mannitol solution. The vial breakage was induced by the mannitol crystallization which produced high hoop tensile stresses, exceeding the practical strength of the vial. Table 1 shows the percent breakage for each pedigree. Valor vials, due to high practical strength, were at least 40 times less likely to break than conventional borosilicate vials under these freeze-thaw conditions.

TABLE 1
FREEZE-THAW GLASS BREAKAGE RATES USING AGGRESSIVE 15% MANNITOL WITH 50% FILL VOLUME OF 2R, 6R, 10R, AND 30R CONVENTIONAL BOROSILICATE VIAL COMPARED TO 2R, 6R, 10R, AND 30R VALOR® GLASS VIALS. *STUDY USED 1,000 VIALS FOR EACH GLASS TYPE AND VIAL FORMAT.*

CONVENTIONAL BOROSILICATE | VALOR GLASS

FIGURE 4
6R CONVENTIONAL BOROSILICATE VIAL WITH A BREAK PATTERN TYPICAL OF LYOPHILIZATION FAILURE FROM THE FREEZE-THAW STUDY AND 6R VALOR VIALS FROM THE SAME STUDY

VERIFICATION OF BREAKAGE RESISTANCE PERFORMANCE ON A PHARMACEUTICAL MANUFACTURING LINE

To demonstrate the damage and breakage resistance of Valor Glass vials during an industrial lyophilization process, a large-scale trial was performed on commercial filling and lyophilization equipment. Approximately 120,000 3mL Valor vials were washed, depyrogenated, filled, stoppered, lyophilized, capped, and inspected during this trial. Standard process metrics including cosmetic reject rate, qualitative cake cosmetics, and residual moisture level were monitored throughout the trial, and Valor vials were well within the normal manufacturing variation for these metrics. No Valor vials broke during the lyophilization process, verifying the results from the laboratory freeze-thaw study and demonstrating expected performance in a real-world application.

To further assess damage resistance and potential for glass breakage, strength comparisons of Valor Glass vials and conventional borosilicate vials were analyzed by horizontal crush testing on 100 borosilicate and 100 Valor vials before and after filling line processing. As shown in **Figure 5**, the "as received" borosilicate vials have lower starting strength than the Valor vials and are further weakened by damage introduced during the filling line processing. The Valor Glass vials maintain their high initial strength even after transport, handling, filling, and the rigorous industrial lyophilization process.

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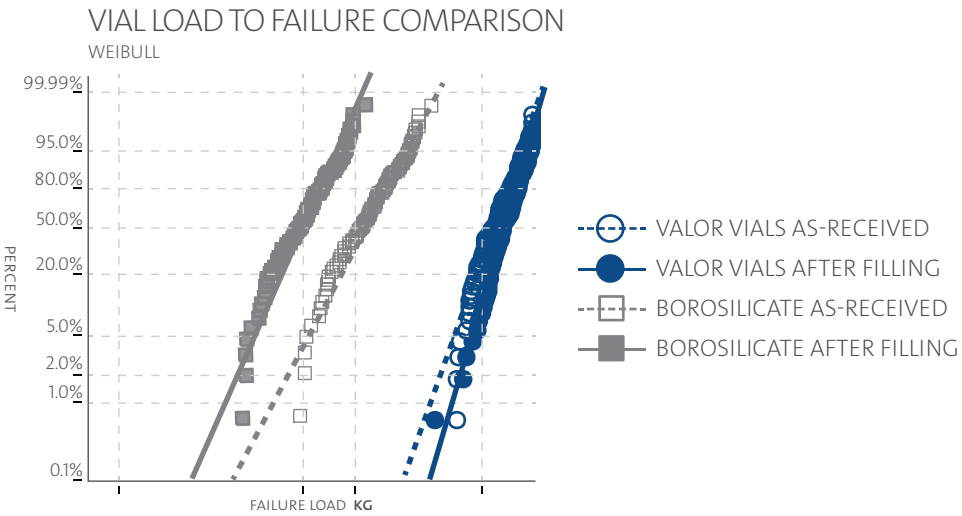

FIGURE 5
HORIZONTAL CRUSH STRENGTH TESTING COMPARISON FOR PRE- AND POST-FILLING LINE PROCESSED CONVENTIONAL BOROSILICATE AND VALOR® GLASS VIALS, DEMONSTRATING THE DAMAGE RESISTANCE OF VALOR GLASS TO THE RIGORS OF AN INDUSTRIAL LYOPHILIZATION PROCESS

TESTING SUMMARY

Based on laboratory studies and pharmaceutical manufacturing trials, Valor vials deliver superior performance compared to conventional borosilicate vials in lyophilization processes. Valor® Glass was 40 times less likely to break than conventional borosilicate vials during aggressive freeze-thaw testing. Engineering trials on commercial lyophilization lines produced no breakage with Valor vials, and testing *post-processing* indicated no strength degradation. Conversely, borosilicate vials exhibited significant weakening, linking the laboratory results to a real-world application.

VALOR GLASS – A SUPERIOR SOLUTION FOR LYOPHILIZED DRUG PRODUCTS

The process of freeze-thaw, cryogenic preservation and lyophilization of pharmaceutical products requires a robust container that withstands extreme temperatures and resists damage and breakage. Glass vial failures due to damage and breakage are a source of product loss and result in higher process costs, delays due to destruction of product, and possible drug shortages.

Compared to conventional borosilicate vials during the lyophilization process, Valor vials significantly reduce damage and breakage and may lower manufacturing cost. The chemical strengthening process for Valor vials imparts compressive stress on the glass surface that typically exceeds the tensile stresses generated in the freeze-thaw process dramatically reducing the potential for breakage.[5] In addition to protecting the vial surface, Valor Glass' low coefficient of friction coating demonstrates faster chamber fill during the lyophilization process and improved manufacturing efficiency with higher run and uptime rates.[11] Overall, Valor Glass vials demonstrate superior performance in low temperature processes compared to conventional borosilicate. The advanced parenteral glass packaging technology of Valor Glass enables the potential for reduced start-to-finish times and improved yields which may reduce total cost of quality as well as manufacturing cost.

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