Here, Boris Schmid, Corporate QA Director, and Daniele Zuccato, R&D Project Manager, both of Stevanato Group, describe studies conducted to investigate delamination of Type I glass containers, and outline the company’s resulting recommendations for mitigating and predicting the risk of delamination.

The delamination of glass when it is exposed to certain environments, is a very well-known phenomenon. For instance, the occurrence of flakes in soda-lime glass bottles intended to get into contact with food and beverages is documented since the early 1940s. In that case, storage of the empty bottles under uncontrolled conditions of humidity and temperature were found to be a key factor.\(^1\)\(^2\)

The most recent cases of product recall due to the presence of particles in the filling liquid,\(^3\) have involved Type I glass containers carrying formulations of active pharmaceutical components with known ability to corrode glass and to dissolve the silica matrix. As this action is strongly affected by time and temperature, flaking may become visible only after a long incubation during storage and requires systematic monitoring to be detected at an early stage.

Reducing the risk of delamination is therefore a serious problem as one has to consider and keep under control all the production stages, including the optimisation of the conversion process, the choice of the most appropriate glass type as a function of the chemistry between glass and the parenteral solution, the filling operations and the shelf life conditions of the product. Therefore the industry is challenged together with the pharmaceutical companies to investigate in order to limit the risk for the patients.

Many open questions require a precise answer. For example: How can we predict delamination? Are European Pharmacopoeia (EP) titration values a reli-
able indicator of delamination resistance? Which glass types are more suitable for which preparations? What can we do along the supply chain in order to mitigate delamination risk?

To answer these questions and to understand in detail the delamination phenomenon, one year ago Stevanato Group started a study of a stepwise approach in collaboration with external institutional laboratories. The aim of the study was to highlight the influence of key parameters like the tubing glass raw material, conversion process and filling conditions.

As a first step, we investigated the raw material in order to reduce risk for delamination. The interaction between several glass types in contact with different extractants, including slightly alkaline preparations, was studied. Investigations were carried out to establish whether there was a correlation between EP titration values and evidence of delamination, as surface alkalinity of the finished products, based on ISO or EP testing for instance, is often used to characterise the influence by the conversion process.

Several Types of borosilicate tubing glass, both sulfur treated and untreated, were tested in contact with different extraction media for repeated autoclave cycles of 1h at 121°C. The propensity for delamination was observed by measuring the SiO\textsubscript{2} concentration in the extraction solutions using Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES). The altered surface was evaluated by a colorimetric method and SEM micrographs, while the presence of particles was monitored by optically assisted visual inspection.

Based on these studies, including an extensive design of experiments, we published some recommendations to mitigate the risk for glass delamination focusing on raw materials and sulfur treatment in combination with buffer solutions (see Box 1: “Recommendations on Delamination Risk Mitigation”).

We also highlighted that evaluating EP values without considering the influence of the nature and the treatments of the glass as raw material, may be misleading. It is well known in fact, that low expansion borosilicate glass (expansion 33) or sulfur treatments will lead to a lower surface alkalinity \textsuperscript{57} but low ISO and EP values are not always a guarantee against the risk of delamination, for instance when the filling liquid is an alkaline solution \textsuperscript{7} and/or a corrosive organic acid like citric acid.\textsuperscript{8}

As a second step, we wanted to develop a test protocol which could be useful for delamination prediction. The protocol was tested on empty containers directly after conversion as well as on filled containers after a prolonged storage time. The results were compared with data from similar tests made on delaminated filled containers. The conclusions developed by this study \textsuperscript{13} are useful to provide both to pharmaceutical manufacturers and glass converters with information needed to help prevent glass delamination and give some indication about the delamination resistance of glass containers. The colorimetric test is a powerful method which can be used immediately after production in order to put in evidence a properly controlled thermal process or an early alteration of the inner glass surface. In combination with further accelerated ageing test, Stevanato Group has an effective tool to control the delamination characteristic of the empty container before filling (see Box 2 on page 42: “Recommendations on Delamination Prediction”).

As a third step, we applied the abovementioned protocol to containers obtained in the Stevanato Group conversion lines after a careful controlled modification of the conversion parameters. It is well known that forming the container with a tightly controlled process has an overall positive impact on the delamination characteristic as it creates less thermal stress that could lead to the formation of enriched silica layers.

The flame settings on finish and bottom forming, machine speed and annealing conditions were identified as the most critical parameters. For each of these parameters, we purposely created a stressing environment for

---

**Figure 2: Result of Colouring Agent Test Showing Strong Colouration of Altered Glass Surface After Accelerated Ageing Test Using 0.9% KCl as Extraction Solution.**

**BOX 1: RECOMMENDATIONS ON DELAMINATION RISK MITIGATION** \textsuperscript{NOTE 2}

Delamination prevention requires a proper selection of the glass tubing raw material combined with a thermally controlled converting process.\textsuperscript{Note 3} Exhaustive information about the intended use of the container is essential. With these conditions in mind, the following recommendations can be given:\textsuperscript{Note 2}

For low pH formulated drugs (pH <7.0), aqueous neutral solutions

Any kind of Type I glass container can be used. We would recommend that the glass containers shall meet Pharmacopoeia specifications before any specified sulphur treatment is applied. Furthermore the sulphur treatment, if required by the client, should be designed so as to guarantee that the modified surface layer is reduced to the minimum necessary thickness.

For high pH formulated drugs (pH >8.0)

In-house testing of high silica borosilicate (expansion 33) and sulphur treated vials in contact with alkaline extraction solutions, showed a steep increase of undissolved silica particles.\textsuperscript{9} We recommend the use of untreated normal borosilicate glass (expansion 51) and possibly reduction of the exposure time.

For drug buffered with silica complexing agents (e.g. organic acids like citrate, tartrate, glutarate, EDTA etc)\textsuperscript{10,11}

As these acids are known to behave as strongly alkaline solutions, we recommend to use untreated normal borosilicate glass (expansion 51) and to possibly reduce the exposure time. Heat treatments and final sterilisation are additional risk factors.

For drug buffers with a high ionic strength (high NaCl or KCl content)\textsuperscript{11,12}

We recommend the use of untreated normal borosilicate glass (expansion 51). The use of sulphur treated vials is to be restricted to preparations with pH around 7 or lower.
the glass surface during conversion process. The inner surface of the containers produced was analysed immediately after production with the combined test protocol consisting of colorimetric test, SiO₂ concentration in the extraction solution, and SEM method.

The result confirmed the significant influence of the critical process parameters mentioned on the delamination characteristics of the inner glass surface. Therefore it is important using appropriate burner- and forming technology and to keep machine speed, flame positions and energy constant during forming, and to control the annealing conditions.

Stevanato Group has a long tradition and large experience in producing glass on vertical indexed machines, of our proprietary design and production, using the appropriate technology. As a consequence, the containers have potentially a lower risk for future delamination.

Ageing tests under real conditions, involving both glass converter and pharmaceutical manufacturer, should be conducted in order to proof the delamination resistance of the containers where required.

**NOTES:**

1. Glass containers from a controlled thermal forming process, such as the Ompi process.
2. As the recommendations are based on a specific testing design by Stevanato Group in collaboration with an external laboratory, they are not covering all possible parameters and shelf life conditions which can be met by any filled product. Therefore it is necessary to evaluate and to approve each application based on real ageing and stability tests established by the customer.

**REFERENCES:**

EZ-fill™

Ready to fill
The EZ Way

EZ-fill syringes, vials and cartridges is the scalable cGMP industrial solution which combines expert glass production and container processing in flexible “ready to be filled” packaging.

Nuova Ompi

glass division
Stevanato Group

www.stevanatogroup.com
nuovaompi@stevanatogroup.com