Thus, special attention has to be taken to minimize the interactions between the drug and the formulation compounds on one side and the glass surface on the other.

Extractable and leachable compounds from the glass can directly influence the formulation of modern active pharmaceutical ingredients (API) based on biomolecules (e.g., recombinant antibodies) whose activity is sensitive to any changes of the storage conditions. Protein adsorption kinetics can be very quick, saturation of the surface taking place in the range of a few hours (2,3). The result is not only a loss of active compound, especially for highly diluted APIs (4–6), but also conformational changes that can occur depending on the stability of the biomolecule (7). These changes can lead to the formation of protein aggregates that might trigger immune responses.

Possible implications are therapy failure and severe diseases (8). Silicone oil can also induce aggregation with the described consequences for the health of a patient (9). Such oils are used to lower the surface energy to minimize the residual volume of highly concentrated drug solutions like antibodies that exhibit a high viscosity (10). Furthermore, in prefilled syringes, a lubricant film is generated to produce a smooth gliding of the piston down the barrel.

Therefore, several demands are made on the usage of glass as a container for (bio)pharmaceuticals:

- Low alkalinity
- Chemical durability
- Low chemical and physical interaction of the container walls with pharmaceuticals ("drug-container interaction")
- Complete removal of dosage (by application of hydrophobic coatings)
- Robustness against sterilization processes (high-energy radiation, ethylene oxide (ETO), water vapor)
- Robustness against mechanical and thermal stresses

If the drug is preserved by freeze-drying (lyophilization) to enhance its lifetime, mechanical requirements on the glass container are also important. For drugs processed by lyophilization, glass is the most frequently used material for vials.

LYOPHILIZATION: REQUIREMENTS ON GLASS VIALS

The three process steps of lyophilization (i.e., freezing, primary, and secondary drying) and the subsequent shipment and storage require a high mechanical strength of a glass vial:

1. Freezing: During freezing, the aqueous solution of protein and excipients is transferred from the liquid to the solid state. While water starts to expand at temperatures below 4°C and the volume fraction of ice to water is about 11% (11), the transformation of water molecules to crystals inside a vial, as well as the crystallization of other excipients in the formulation, causes a mechanical load on the walls of the glass vial (12). Some biomolecule formulations that freeze to amorphous solid states lead to glass vial breakage during cooling (13), which is hypothesized to be caused by a sudden detachment of the frozen formulation plug off the walls of the glass vial resulting in a mechanical shock wave through the glass walls (13).