sugar alcohols, a thermally induced crystallization during cooling can be simulated (12,16), whereas protein formulations are appropriate to investigate the thermal expansion behavior of pharmaceuticals freezing in an amorphous state (13). With these kind of experiments, the simulation of the mechanical load during the lyophilization process is more realistic than for burst-pressure testing using water as the pressure medium (Fig. 3). However, the determination of the stresses requires extensive strain-gauge techniques and is less precise.

Thermal Shock Testing

Thermal shock testing is an additional tool to burst-pressure testing to determine the strength of glass containers: A sample is exposed to an instant temperature difference, thus "shocked" either by rapid heating or cooling. This sudden temperature change is accomplished by quenching (e.g., from elevated temperature into an ice bath) or heating up (e.g., from low temperature into a hot liquid bath) the specimen. Because of the rapid temperature change, an enormous temperature gradient is caused within the glass. This temperature gradient can cause strong local stresses due to differing thermal conduction caused by the geometry of the sample (e.g., wall thickness of a glass vial), leading to different thermal expansions of cool and hot regions. Thermal shock testing is an integral testing method, meaning the whole sample is stressed simultaneously at the same time, leading to failure at the weakest point of each specimen.

Fracture Statistics

For strength testing, an intentional mechanical loading in a testing range is required until breakage of the sample. Typically, the strength values for failure during testing (testing range) are much higher than the values that appear to the product in usage (usage range). Nevertheless, strength testing with excess load is necessary to acquire information about the distribution of strength data for every particular product.

The strength data from the tests is plotted in a statistical plot (see Fig. 5 as an example assuming a Weibull distribution of the data): The cumulative failure probability F is plotted versus the burst pressure p. Other strength testing units (on the abscissa/x-axis) can be, for instance, stress σ, temperature difference ΔT, or force F, depending on the technique for strength testing.

The testing range of the experiment is defined by the range of the failure data (in Fig. 5, a testing range between 60 and 125 bar is applied). The dashed lines in Figure 6 enclose the strength data and mark the 95% confidence bounds (i.e., the true distribution of this sample lies within these confidence bounds with a probability of 95%). The axes of the statistical plot in Figure 5 are not linear but intentionally biased. If data can be described by a particular statistical distribution (in this case Weibull distribution), the biasing of the axes leads to a linear arrangement of the data. So plotting strength data in a statistical plot is used to qualitatively check for a particular statistical distribution. To check quantitatively whether strength data can be described by a particular statistical distribution, numerous hypothesis tests ("goodness-of-fit tests") are available (17).

If an appropriate statistical distribution is accepted, the fracture probability F can be calculated for any load by extrapolation. For instance, the fracture