TABLE 5 Effect of Variable Residual *tert*-Butanol in CAVERJECT Sterile Powder on T_g and the Degradation Product (PGA_1) Formation After Nine Months at 25°C

% *tert*-Butanol	Estimated[a] T_g (°C)	PGA_1 (μg/mL) after 9 months at 25°C
1.4	97	1.0
1.4	97	0.9
4.0	79	3.1
4.0	79	3.2
5.1	71	4.0
5.2	71	3.8

High residual *tert*-butanol caused decreased T_g and increased degradation.
[a]Estimated using Gordon–Taylor equation (104).

the secondary drying phase did not significantly reduce the residual *tert*-butanol level in the freeze-dried sucrose cakes. Similar results for lactose dried from *tert*-butanol/water have been observed. Other solvent systems may be behaving differently than *tert*-butanol since freeze-drying of imexon from neat DMSO produced crystalline imexon; however, the residual DMSO content was relatively high at 4.6% (4).

It should be noted that the level of residual solvent may have an impact on the stability of the freeze-dried product. The residual solvent can act as a plasticizer at low levels, decrease the glass transition temperature (T_g) of the dry matrix, increase its molecular mobility, and thereby affect stability of the lyophilized powder. CAVERJECT Sterile Powder, which was freeze-dried from *tert*-butanol/water, could produce variable residual *tert*-butanol levels for non-annealed samples. The different levels of residual *tert*-butanol in the dried matrix would be expected to affect the T_g, as predicted by the Gordon–Taylor equation (104). Table 5 and Figure 6 show data that illustrate the impact of different residual *tert*-butanol levels on the T_g and stability of CAVERJECT [as evidenced by the formation of the degradation product (PGA_1)]. The increase in residual *tert*-butanol appeared to plasticize the dry cake, decrease the T_g, and increase the degradation rate.

Thermal Treatment (Impact of Annealing)

It is noteworthy that the level of residual solvent remaining at the end of the freeze-dry cycle can be significantly impacted by use of thermal treatments (e.g., annealing) of the frozen solution prior to initiation of the drying phase. This effect is illustrated by studying the impact that process conditions had on the residual *tert*-butanol levels remaining in CAVERJECT Sterile Powder. This product contains a predominantly lactose base and is lyophilized from a 20% vol/vol *tert*-butanol/water solution. Normal freezing by loading on precooled (i.e., −40°C) shelves followed by lyophilization produced a bimodal distribution of residual *tert*-butanol levels (Fig. 7). The majority (94–97%) of a typical lot contained residual *tert*-butanol levels in the range of 1% to 2%. However, the remaining 3% to 6% of the lot contained *tert*-butanol levels ranging from 3.4% to 5.5%. A tighter control of the residual alcohol level was achieved for this product through the addition of a thermal treatment step (i.e., annealing) during the freezing phase to control metastable forms of solvents that might form. The differential scanning calorimetry thermogram of the CAVERJECT frozen