



**FIGURE 6** The impact of the estimated glass transition temperature on degradation product (PGA<sub>1</sub>) formed for CAVERJECT Sterile Powder after nine months at 25°C. *Abbreviation:* TBA, tertiary butyl alcohol.

solution (unannealed and annealed) is illustrated in Figure 8. The annealing likely enabled any remaining unfrozen *tert*-butanol hydrate to crystallize and produce a more uniform frozen product. The presence of the amorphous solute such as the lactose probably was the cause of the presence of the metastable unfrozen *tert*-butanol since it would be expected to inhibit the crystallization of the *tert*-butanol during cooling (80,105). The effect of this thermal treatment on the residual *tert*-butanol was rather dramatic (Fig. 7). The resulting *tert*-butanol levels were on average slightly lower (0.8–1.1%), much tighter, and no values exceeded 1.3%. A similar annealing technique was employed during the freezing phase for apidine in a 40% vol/vol *tert*-butanol/water system and for tobramycin sulfate in a 5% *tert*-butanol/water system prior to lyophilization (6,10,67). Annealing of cefazolin sodium in solutions isopropanol/water, ethanol/water, and *tert*-butanol/water (followed by lyophilization) all produced lower residual solvent levels than non-annealed samples (25). However, only the *tert*-butanol was able to truly crystallize during the thermal treatment. It also produced the lowest residual solvent level (<0.2%). It was postulated that, when annealing compounds that crystallize as hydrates, one must be aware that the dehydration that occurs during the lyophilization process may produce a crystalline hydrate to amorphous anhydrate transition and negate the utility of the cosolvent (25).

It is clear from the above discussion that the formulation scientist must evaluate the impact of the process conditions on the developing freeze-dried formulation to adequately control the residual volatile organic present at the end