proteins through a solvent damaged cell membrane. Neat *tert*-butanol exhibits excellent bactericidal properties against *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*. There are also reports of several organic solvent-resistant organisms (90,91). The presence of an organic solvent, therefore, does not guarantee that the bulk solution will have adequate microbicidal properties. Each formulation must be evaluated as to its growth-promotive nature to determine the appropriate aseptic manufacturing requirements. If the solution is sterilized by filtration then the prefiltration bioburden must be evaluated and an appropriate holding time for the unfiltered solution qualified.

CONTROL OF RESIDUAL SOLVENT LEVELS

The retention of volatile components such as organic solvents during freeze-drying has been well described in the literature (5,92–100). Many of the organic compounds in the food aroma have a vapor pressure higher than water. However, a significant number of these compounds remain with the freeze-dried cake after lyophilization. Two theories that are used to explain this phenomenon have been described as "selective diffusion" (100) and "microregion entrapment" (98). The retentive behavior for model amorphous carbohydrate systems, which were freeze-dried from various volatile organic solvents, was studied by Flink and Karel (94). They found that the volatile retention for organic solvents (acetone, methyl acetate, ethanol, *n*-propanol, isopropanol, *n*-butanol, *tert*-butanol, and 1-pentanol), which were freeze-dried in maltose, sucrose, or lactose ranged from 1.4% to 3.3%. The retention levels were similar for volatiles of different vapor pressures. The microregion entrapment theory postulates that the retention is not due to adsorption to the dried material. The solvent retention appears to occur in localized regions where the volatile was initially frozen. These regions occur on a microscale. Increases in the secondary drying conditions of temperature or reduced pressure do little to decrease the volatile retention level. The volatile retention shows no competition with water vapor for sorption sites, which might be indicative of different modes of interaction with the amorphous carbohydrate. The previous statement appears to be true up to a point as long as the samples are kept dry. Upon humidification of the dried carbohydrate containing the entrapped volatile organic, there appears to be a critical humidity condition that results in a corresponding moisture level where the volatile organic is rapidly released. An example of this effect is illustrated by the humidification of maltose, which had been freeze-dried from either isopropanol/water or *tert*-butanol/water. Both exhibited a trend whereby as the moisture content reached approximately 8% to 9%, the residual alcohol content dropped significantly (96). Structural changes in the cake due to moisture absorption, especially during cake collapse, can result in rapid loss of the entrapped volatile. Others noted that residual *tert*-butanol in sugars (e.g., sucrose, trehalose, and inulin) could be reduced by exposure to moisture vapor (87). The *tert*-butanol removal from the sucrose and trehalose was accompanied by crystallization of the sugars; however, the glassy inulin remained amorphous. The volatile retention appears to be related to hydrogen bonding to the amorphous carbohydrates. As the hydrogen bonds are broken, such as at certain moisture levels, the volatile loss accelerates. The selective diffusion model predicts that as the water content for carbohydrate systems decreases, the ratio of