degradation that are dependent on the kinetics of the degradation mechanism. The presence of the various levels of organic solvent can have a profound effect on the chemical stability. Those drug candidates that are very labile in aqueous solutions may require improved stability to achieve an acceptable level of degradation during manufacture.

Early efforts to freeze-dry an antineoplastic agent (1,3-bis(2-chloroethyl)-1-nitroso-urea) from an ethanol/water solution were initiated because of the rapid degradation in aqueous solution and improved solution stability in ethanol/water solutions (48). Unfortunately freeze-drying this product in the ethanol/water cosolvent system proved to be unsuccessful due to potency losses and unacceptable clarity. Flamberg et al. (48) suggested that an alternative process to freeze-drying solvent systems containing ethanol would be to use low-temperature vacuum drying.

The antitumor drug (SarCNU) was so unstable in aqueous solution that it needed to be freeze-dried from neat *tert*-butanol to prevent degradation during processing (49). The first-order degradation rate noted for SarCNU was 57 times faster in water compared with that in neat *tert*-butanol. Other solvents (e.g., acetic acid, DMSO, or *tert*-butanol/water mixtures) could also be used to freeze-dry SarCNU; however, the solution stability in these solvents was significantly less stable than in neat *tert*-butanol (49). DMSO has been used to stabilize solutions of imexon sufficiently to minimize degradation prior to lyophilization from this solvent system (4). The use of *tert*-butanol (40% wt/vol) was also evaluated for its impact on imexon solution stability; however, neat DMSO was shown to be superior (4).

Another anticancer agent (Rhizoxin), which was freeze-dried from *tert*-butanol (40%), benefited from an enhanced stability in the cosolvent system compared with water (47). A similar observation of improved solution stability in a *tert*-butanol/water cosolvent prior to producing freeze-dried product was noted for the bladder cancer agent (EO-9) (7). Both of these examples enabled manufacture of the product with minimal degradation during processing.

Alprostadil (the active ingredient in CAVERJECT Sterile Powder) has been successfully freeze-dried from a *tert*-butanol/water solution. The first-order degradation rate constant of alprostadil in 20% vol/vol *tert*-butanol/water (k = 0.0011/day at 25°C) was significantly reduced compared with water buffered at the same pH value (k = 0.0041/day at 25°C). This data is consistent with the claims of extraordinary stability of prostaglandins in *tert*-butanol (50). This decreased degradation rate enables the manufacturing unit operations to be performed at ambient conditions without requiring cooling of the solution during manufacture. Additionally, it adds flexibility in scheduling these various operations because the solution degradation has been minimized.

The formulation of trecetilide fumarate, a sterile injectable in clinical development for treatment of arrhythmias, also involved freeze-drying from a *tert*-butanol/water mixture (51). Kinetic analysis showed solution degradation occurred by a process of defluorination through SN_1 substitution and E_1 elimination, both proceeding through the same carbonium ion intermediate. Since factors such as ionic strength, buffer type, solution pH, and drug and buffer concentrations did not significantly affect degradation rate, destabilization of the fluoride leaving group was one of the few methods left to control this reaction. Use of tertiary butyl alcohol as a cosolvent slowed solution state degradation by a factor of approximately 4 to 5. This significantly increased the probability of