freeze-dried products (22). Undoubtedly, terminal sterilization is a reasonable request from a microbiological safety standpoint. However, there are major technical and scientific challenges associated with the application of terminal sterilization to freeze-dried products. Dry powder heat sterilization, which is the first technique required for evaluation, is not expected to be compatible with freeze-dried protein products because of the high temperatures involved (usually $\geq 160^{\circ}C$). Sterilization by ionizing irradiation may be more feasible from a technical standpoint; however, there are major challenges associated with this technology as well. Proteins are known to be sensitive to ionizing radiation (23,24), although the extent of degradation might be lower than that associated with the high-temperature treatment during dry heat sterilization. Additionally, lyophilization stoppers are often incompatible with irradiation whereas radiation-resistant stoppers may not be compatible with lyophilized products that require special rubber formulations with low water retention (25).

IMPACT AND CONTROL OF MOISTURE

A critical aspect of most freeze-dried products is an evaluation of the impact of residual moisture on product quality. Since the freeze-drying process typically produces amorphous systems, residual moisture can have a profound effect on the glass transition temperature of freeze-dried products. The presence of residual moisture can plasticize the dried cake and greatly increase the molecular mobility of the solid and water (26). This is especially a concern if the dried product is stored near or above its T_g. The presence of moisture can promote a variety of "solid-state" interactions and lead to instability of the final product (27). Therefore, the impact of variable moisture levels on chemical and/or physical stability is paramount to enabling the appropriate moisture specification to be set. Consequently, it is important to establish a rationale for the appropriate residual moisture specification for each freeze-dried product based on critical product characteristics such as chemical or physical stability. This moisture specification rationale should be included as part of the regulatory file for new drug applications. Typical moisture specification limits for most freeze-dried products range from 1% to 5%; however, there may be exceptions that fall outside this range. It is also noteworthy that there may be both a time of release moisture specification and a separate shelf life moisture specification. Data should be generated to justify both sets of moisture specifications.

Proper control of moisture for the product throughout its shelf life is best met by understanding the sources of moisture for the dried material. The secondary drying conditions for the freeze-dry cycle usually determine the residual moisture level at the end of drying (assuming no cake collapse occurred during the primary drying phase of the freeze-dry cycle). Use of lyoclosures with packages that allow internal stoppering of the package enable tight control of residual moisture after drying is completed. It should be noted that some dual chamber container closure systems allow internal stoppering within the freeze-dryer; however, others do not have this capability. Therefore, those products that are sealed outside of the dryer (e.g., externally stoppered vials, some DCCs, or DCVs, etc.) may absorb atmospheric moisture before they are properly sealed. The rate of moisture uptake