Additional Degradation Processes at Higher Temperatures

At higher storage temperatures, additional degradation processes can become significant that are irrelevant at lower and conventional temperatures of storage. These additional degradation processes can include Amadori products arising from reactions between protein and carbohydrates and often resulting in a discoloration of the material stored at elevated temperatures. If statistically significant, these additional processes can prevent the experimental data from being fitted to the degradation equation since there is no longer a linear relationship between ln(degradation rate) and the reciprocal of absolute temperature.

When not statistically significant, such additional processes can lead to an overestimation of the rate of degradation at conventional storage temperatures by using the combined degradation at the higher temperatures. This is particularly the case if the degradation study has not continued long enough for significant degradation to occur at the lower storage temperatures, when undue weight is placed on the data from the higher temperatures.

Temperature Effects on the Integrity of the Container

If vials are used as the container of the material, high or low temperatures may affect the physical properties of the stopper and thus the integrity of the seal it makes with the neck of the container. This should be investigated prior to their use (6,7).

Example of Accelerated Degradation Studies on a Biological Standard

The use of accelerated degradation studies is illustrated in Figure 17 by reference to factor VIII concentrate stored at −20°C: potency was tested using the European Pharmacopoeia chromogenic assay.

Data was fitted using the Arrhenius equation

$$\ln(K_{\{T\}}) = A + B/T,$$

where

$K_{\{T\}}$ is the degradation rate at the absolute temperature T, relative to the rate at the reference temperature, and

A and B are constants.

Maximum likelihood estimates of the constants A and B are as follows:

A	24.24
Asymptotic error of A	1.61
B	−7244.98
Asymptotic error of B	502.27
Asymptotic covariance of A and B	−810.90

The Chi-square test statistic for the predicted versus observed activity remaining at the various time points is 4.41 for 5 degrees of freedom. At the 5% level, the predicted remaining activities are not significantly different from the observed remaining activities.

The predicted potency loss is shown in Figure 17, indicating that at a storage temperature of −20°C, the standard had good stability with low degradation rate.