temperature, if the material cannot be assayed without delay, it should be stored at the reference temperature.

Models

It is usual to model the degradation of materials using the Arrhenius equation

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

or the Heyring equation

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

where

- $K\{t\}$is the degradation rate at the absolute temperature T (Kelvin), relative to that at the reference temperature; and
- A and B are constants.

The Heyring equation is said to have a slightly stronger theoretical basis. Both models assume a unimolecular, single mechanism of degradation of first-order kinetics.

By determining the relationship between the degradation rate and temperature using samples stored at a range of higher temperatures of storage, the degradation rate at lower, that is, conventional, storage temperature can be predicted using these models. For the computational methods used refer to the work of Kirkwood et al. (36,37).

Confidence Limits of Prediction

The random error in potency estimates is assumed to be log-normally distributed.

The upper 95% confidence limit is derived from the equation

$$K\{t\}'' = K\{t\} + (C.\text{se}Kt),$$

where

- $K\{t\}''$ is the upper 95% confidence limit of the degradation rate $K\{t\}$;
- C is a constant; and
- se$K\{t\}$ is the standard error of $K\{t\}$.

It is not possible to determine a value of C to be used in all cases. The value of C depends on the total statistical weight of the study (the reciprocal of the variance of $\log_{10}$ estimates of relative potency, from which the mean relative potency is obtained), that is,

- for a total statistical weight of 30,000 or more, and where at least 25% degradation has occurred at temperatures of 37°C or greater, a value for C of 4 (with 3 elevated temperatures) or of 3 (with 4 elevated temperatures) or of 2 (with 5 elevated temperatures) should be used, and
- for a total statistical weight of less than 30,000, a value for C of 5 should be used.