Modeling Strategies for Accelerated Stability Studies

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Accelerated Stability

- Monitoring and determining the stability of drug substances and drug products are critical activities in the drug development process. Stability studies are by nature long (months to years); therefore, it is important to develop models that allow pharmaceutical scientists to obtain chemical stability information fast and reliably. For this, accelerated stability protocols and mathematical models have been developed for rapidly obtaining the necessary information to determine the shelf-life of the product. Shelf-life of a pharmaceutical product is the period of time from its manufacture date that remains within its approved specifications while stored under defined conditions. Generally, the shelf-life is determined for the 25°C/60% RH storage conditions.
- Accelerated Stability protocols consist of exposing drug substance and drug product to different combinations of high temperatures and humidity levels. The temperatures range typically from 50°C to 80°C and the humidity can be as low as 10% to as high as 75%. The exposure time can range from less than 7 days to 3 months; however, most protocols last 14 to 21 days.
- The shelf-life is obtained by extrapolation from the high temperature/humidity based protocols; hence, it is imperative to understand the underlying statistical models and science of the experimental protocols/models applied to get the shelf-life.
- This poster compares two statistical approaches with a commercial program to obtain the necessary parameters to estimate the shelf-life of pharmaceutical products.

Arrhenius Equation

Named for Svante Arrhenius (1903 Nobel Laureate in Chemistry) who established a relationship between temperature and the rates of chemical reaction

$$k_T = k(T) = Ae^{-\frac{E_a}{R \cdot T}}$$

where k_T = Degradation Rate

A = Non-thermal Constant

E_a = Activation Energy

R = Universal Gas Constant (8.314 x 10^{-3} kJ mol^{-1} K^{-1})

T = Absolute Temperature

Historical Notes

1. E.R. Garrett. (1955). Prediction of Stability in pharmaceutical preparations. J Pharm Sci V.44(8) p515-518
2. H.A.McLeod, O.Pelletier and J.A. Campbell. (1958). The Prediction of Expiration Dates for Multivitamin Preparations by Accelerated Storage Tests. Canadian Pharm J Scientific Section V.91: 173–180
3. J.P.R. Toothill. (1961). A Slope-Ratio Design for Accelerated Storage Tests. J Pharm Pharmacol. V.13:75T-86T

Extended Arrhenius Model

Genton & Kesselring Extended Arrhenius Equation

A humidity term (B coefficient) is introduced to account for the effect of relative humidity on rate parameter (1977, Genton and Kesselring[1]).

activation energy; degradation rate; humidity sensitivity factor

$$\ln(k_{T,H}) = \ln(A) - \frac{E_a}{R \times T} + B \times H$$

Pre-exponential factor; gas constant (8.314 x 10^{-3} kJ mol^{-1} K^{-1})

Nonlinear Parameterization of Genton and Kesselring extended Arrhenius Model: King-Kung-Fung (1984)[2]

- Kinetic rate-based reparameterization of the Arrhenius model
- Accommodates zero and first order kinetic models
- Nonlinear regression analysis employed to provide parameter estimates of shelf life, E_a and C_0.
  - Allows direct statistical predictions shelf life using observed values of drug content, **time** and **temperature**
  - Statistical nonlinear numerical modeling leads to appropriate estimates of parameter uncertainty. Lower 95% confidence bound on shelf life parameter chosen for shelf life, consistent with ICHQ1E definition.

The King-Kung-Fung (KKF) model modified to describe the formation of degradant:

$$k_{T,H} = Ae^{-\frac{E_a}{R \times T} + B \times H} \xrightarrow{\text{Let } T=298^oK\ (25^oC),\ H=60} A = k_{298,60}e^{\frac{E_a}{298 \times R} - B \times 60}$$

$$k_{T,H} = k_{298,60}e^{\frac{E_a}{R}\left(\frac{1}{298} - \frac{1}{T}\right) + B(H-60)} \qquad k_{298,60} = \frac{Q - D_0}{t_{SL}}$$

Assuming zero order kinetics, total degradation is: $D_t = D_0 + k_{T,H} \times t$

$$D_t = D_0 + \frac{Q - D_0}{t_{SL}} \times t \times e^{\frac{E_a}{R} \times \left(\frac{1}{298} - \frac{1}{T}\right) + B \times (H-60)} + \varepsilon$$

- Estimate Shelf Life at 25C/60%RH and its uncertainty w.r.t spec = Q
- Parameter estimates are calculated based on the Arrhenius relationship conditional on an assumed zero order kinetic

Linearized Extended Arrhenius Model

Two-stage approach (Garrett,1955)

Assume a zero order kinetic model*

- **Stage 1** : fit a pseudo zero order kinetic model to the concentration measurements versus time:

$$D_T(t) = D_0 \pm k_{T,h} \cdot t$$

(+) if degradant is measured; (–) if API is measured; Common initial D_0 induces correlations between the rate parameter estimates

- **Stage 2** : Model the rate estimates according to Arrhenius relationship:

$$\log k_T = \underbrace{\log A}_{\beta_0} + \underbrace{\frac{E_a}{R}}_{\beta_1} \cdot \frac{1}{T} + \underbrace{B}_{\beta_2} \cdot h$$

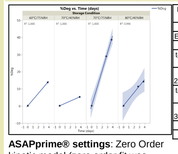
Expressed as linear regression problem (Generalized Least Squares for estimation)

$$\log k_T = \beta_0 + \beta_1 \cdot \frac{1}{T} + \beta_2 \cdot h + \zeta$$

*Garrett assumed separate intercepts for each temperature condition. The common intercept model is due to Toothill.

Two Case Studies

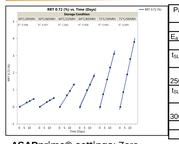
I. Degradant 1 (Upper Specification=3%)



Parameter (se)	ASAPprime®	KKF Model	Garrett Two-Stage
$D_{0(SE)}$	-	0.270 (0.4230)	0.360(0.50)
E_a (kJ Mol^{-1})	105.0 (9.2)	100.5 (3.86)	100.4 (4.4)
B (RH)	0.0585 (0.0047)	0.0569(0.00174)	0.060(0.002)
$t_{50,\ 25C/60\%RH}$ (Days)	164	127	122
Expiry 25C/60%RH	-	72	56
$t_{50,\ 30C/75\%RH}$ (Days)	32	28	26
Expiry 30C/75%RH	-	17	14
MSE	-	0.2139	0.27
lnA (se)	34.8 (3.0)	-	33.2 (1.4)

ASAPprime® settings: Zero Order kinetic model (zero order fit was equivalent to the default fit in this example); RSD = 5.0%; Specification = 3.0%

II. Degradant 2 (Upper Specification=0.54%)



Parameter (se)	ASAPprime®	KKF Model	Garrett Two-Stage
$D_{0(SE)}$	-	0.20 (0.04)	0.071 (0.02)
E_a (kJ Mol^{-1})	85.8 (4.2)	132.9 (6.4)	119.7 (2.0)
B (RH)	0.0044 (0.0013)	0.00773(0.0009)	0.0068 (0.0003)
$t_{50,\ 25C/60\%RH}$ (Days)	204	1705	1163
Expiry 25C/60%RH	-	941	960
$t_{50,\ 30C/75\%RH}$ (Days1)	109	627	473
Expiry 30C/75%RH	-	382	401
MSE	-	0.006	0.001
lnA(se)	28.4 (1.5)	-	40.1 (0.7)

ASAPprime® settings: Zero Order kinetic model (zero order fit was equivalent to the default fit in this example); RSD = 5.0%; Specification = 0.54%

Comparison of Approaches

- Linearized Arrhenius Model (Garrett)
  - Approximations needed to compute covariances, requires GLS approach for appropriate weighting
  - Permits release limits calculation
- Nonlinear Model (King-Kung-Fung)
  - Computationally intensive, convergence can be an issue
  - Fixed initial and rate constants not explicitly estimated
  - Avoids the complications of the two-stage approach
- ASAP*prime*
  - User defined fitting options for error estimation
  - Standard statistical approaches not used for uncertainty limits of parameter estimates
  - Inconsistent comparability with standard statistical approaches

Comparison of Dataset	shelf life estimates (days) from Condition	ASAP*prime* Zer o Order	ASAPprime , KKF and Garrett KKF	Two -Stage Garrett
Deg 1	25C/60%RH	164	127 (72)	122 (56)
	30C/75%RH	32	28 (17)	26 (14)
Deg 2	25C/60%RH	204	1705 (941)	1163 (960)
	30C/75%RH	109	627 (382)	473 (401)

- The uncertainty limits generated by ASAPprime depend on iterative calculations of isoconversion times (time to reach specified limit). It's not clear that they correspond to a frequentist confidence limit.
- Point estimates of zero order models are comparable in 1 case, not in another.
- The algorithms used by ASAPprime can result in outcomes different from those predicted using standard statistical approaches.

Summary

- Accelerated study models are being reassessed and updated through linear and non-linear models
  - The Garrett two stage method has been updated to reflect current technologies
  - King, Kung and Fung model has been extended to include a humidity term
  - ASAPprime shelf life estimates can be different from Garrett and KKF estimates and will be the subject of further study
- Technology is evolving rapidly which will require more sophisticated statistical modelling to assess uncertainty in the expiration dating estimates
- In the future, the science combined with appropriate modeling approaches may be sufficient to justify regulatory labelling.
- Establishing optimal experimental designs is an area of statistical opportunity

[1]Genton D, Kesselring UW (1977). Effect of temperature and relative humidity on nitrazepam stability in solid state. J Pharm Sci V.66(5):676-80
[2]Shang-Ying P. King, Min-Shya Kung and Ho-Leung Fung (1984), Statistical Prediction of Drug Stability Based on Nonlinear Parameter Estimation, Journal of Pharmaceutical Sciences, Vol. 73, No. 5, p.657–662, May 1984