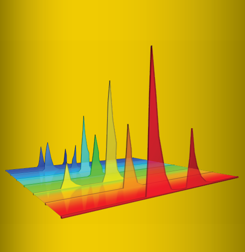

Accelerated Stability Modeling

Characterization of stability performance provides a clear, statistically defendable method for determining accelerated stability.

Understanding the factors that impact stability and then generating product stability knowledge are key considerations detailed in the International Conference of Harmonization (ICH) Q8 (1) development standard as well as the Q1E standard. Accelerated stability analysis is a strategy used to quickly evaluate alternative formulations, packaging and processes; however, it is not always clear how to estimate expiry from the accelerated data.

Understanding the product and process is becoming more of an expectation based on FDA guidance and technical presentations. Building representative product and process models for stability is now considered an essential part of product and process development. Once a product/process model has been established and verified it can be used to support and/or justify potential formulation, process, site, and supplier changes.

Linear and non-linear regression models are recommended in guidance from the health authorities for stability determination. Specifically, ICH Q1E 2.6 General Statistical Approaches states (2):

> *"Regression analysis is considered an appropriate approach to evaluating the stability data for a quantitative attribute and establishing a retest period or shelf life. The nature of the relationship between an attribute and time will determine whether data should be transformed for linear regression analysis. The relationship can be represented by a linear or non-linear function on an arithmetic or logarithmic scale. In some cases, a non-linear regression can better reflect the true relationship."*

Building a product or process stability model typically follows the following steps:

- State the purpose
- Perform a risk assessment to identify the key factors driving the responses of interest (3)
- Develop a stability study design and associated power analysis (4)
- Collect the data
- Fit the model (linear and or non-linear)
- Evaluate the model's usefulness, accuracy, and associated errors
- Evaluate the model's predictive potential and associated errors
- Determine rate of degradation and expiry at nominal conditions and at accelerated conditions
- Verify any early accelerated predictions with long-term stability studies at nominal storage conditions.

Traditionally there has often been an attempt to use the Arrhenius transformation for all accelerated conditions. This approach is good when the assumptions associated with the Arrhenius equation are valid; however, often the Arrhenius transformation becomes the erroneous equation as it does not fit the data and the product or process assumptions cannot be satisfied. The health authorities have issued warning letters to companies that use Arrhenius transforms when the data does not support this method of stability estimation (5). This paper will outline an approach to model and predict linear and non-linear stability data under accelerated and nominal storage conditions. In general, the approach presented in this paper is to model the measured data, understand the scientific rational associated with the degradation pathway (what makes it degrade?), and then generalize the model for multiple accelerated conditions and at the nominal condition.

There are many factors other than environmental that may impact product stability. These factors should be considered as well when developing accelerated and long-term stability and self-life claims:

- Temperature

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Figure 1: Accelerated study power analysis.

Power Analysis	
Significance Level	0.05
Signal to Noise Ratio	2
Error Degrees of Freedom	76
Effect	**Power**
Temperature	1.000
Time (days)	1.000
Temperature*Time (days)	0.997
Temperature*Temperature	1.000

- Humidity
- API concentration
- Water content
- Amount of an excipient
- Processing conditions and/or set points
- Packaging materials/method.

STUDY DESIGN

Proper design of experiments for data collection and factor effect isolation is crucial for building linear and non-linear stability models. All factors should be orthogonal relative to each other and have zero correlation (or near zero). For this simple example, there are multiple time points at multiple temperatures. There are an equal number of samples at each time and temperature condition. Replicates are suggested at each condition to reduce the analytical method variation and to improve the precision of the estimates. In this study, the number of replicates was three at each time point. A power analysis (**Figure 1**) should be performed to assure the stability study has good statistical power (>0.95). This study is a 3*3*9=81 runs, three temperatures with three replicates and nine time points. Simulation can also be used to evaluate study plans and estimate their impact on stability.

ANALYSIS METHOD

The following is the step-by-step procedure for accelerated stability modeling and expiry determination:

Figure 2: Accelerated impurity and temperature.

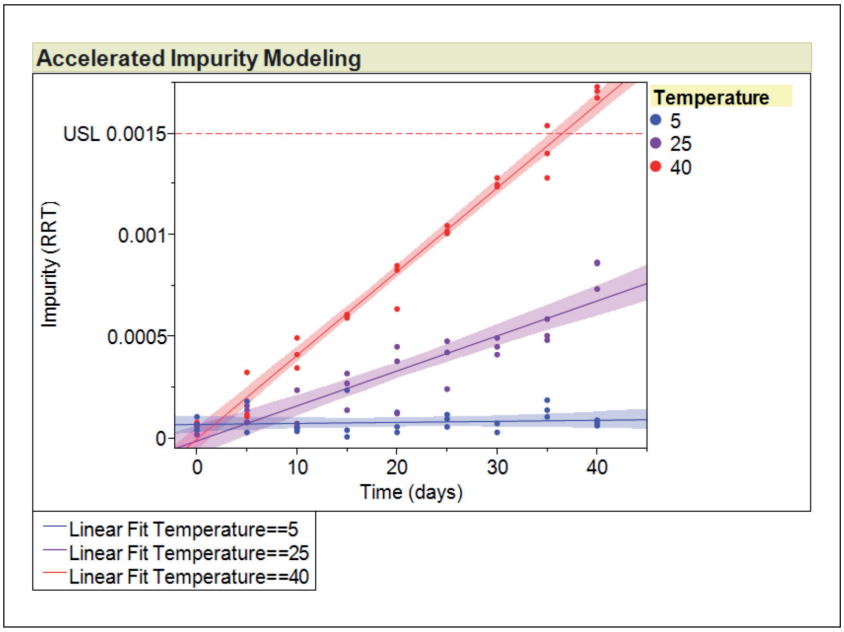
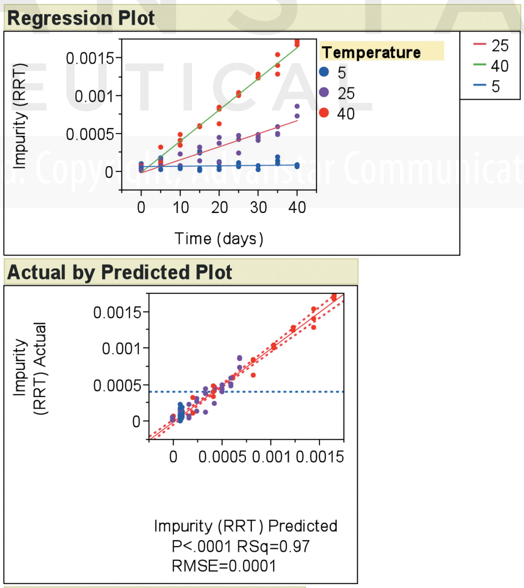


Figure 3: Whole model and effects test.



Summary of Fit

RSquare	0.972154
RSquare Adj	0.970297
Root Mean Square Error	0.00008
Mean of Response	0.00041
Observations (or Sum Wgts)	81

Effect Tests

Source	Nparm	DF	Sum of Squares	F Ratio	Prob > F
Time (days)	1	1	5.23661e-6	818.8813	<.0001*
Temperature	2	2	7.72395e-6	603.9204	<.0001*
Temperature*Time (days)	2	2	3.78336e-6	295.8132	<.0001*

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Figure 4: Inverse prediction of expiry and the lower 95% confidence interval.

Inverse Prediction

Temperature	Specified Impurity (RRT)	Predicted Time (days)	Lower 95%
25	0.0015000	87.706	80.5830
40	0.0015000	36.432	35.4636
5	0.0015000	2779.378	588.7536

Confidence Interval with respect to an expected response

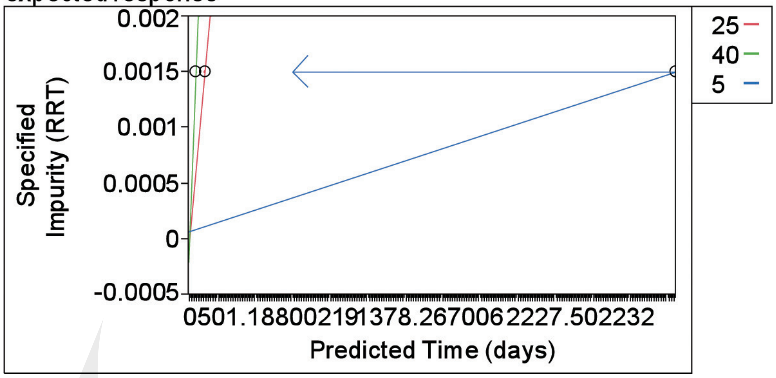

Figure 5: Factor and parameter table.

Temperature	Specified Impurity (RRT)	Predicted Time (days)	Lower 95%	Slope	Acceleration Rate
5	0.0015	2779.4	588.8	0.0000005	1.0
25	0.0015	87.7	80.6	0.0000173	33.5
40	0.0015	36.4	35.5	0.0000413	80.1

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1. Measure the data at multiple time periods and at multiple temperatures. Generate a plot of the data (**Figure 2**) to visualize the relationship of the curves over time. Save the slopes from the curve and place them in a table. Examination of the slopes will indicate if the environmental factor accelerates the rate of change/degradation.
2. Use a multiple factor analysis of covariance (ANCOVA) model to fit the data. Examine the effects test (**Figure 3**) to make sure all terms in the model are significant. The inverse prediction (**Figure 4**) will provide the expiry and the 95% lower confidence interval. Also examine the whole model to determine the RSquare and the quality of the ANCOVA model. Check the residuals to make sure no hidden factor has entered into the study.
3. Save the expiry and the 95% predictions (**Figure 5**) at each temperature into a table. Acceleration rate is the ratio of each slope at temperature to the nominal storage condition.
4. To build a generalized model (**Figure 6**) of how temperature accelerates the rate of degradation and expiry, fit a model of temperature to the coefficients (slopes), expiry, and 95% confidence interval (CI) and acceleration rate. Models may be linear or non-linear in their fitting parameters. Make sure the models selected makes good scientific sense and can be generalized. Modern software programs make this easy to do.
5. Save the equations for the fit for the 95% CI, expiry, acceleration rate, and the slope.

Predicted Slope=
(-0.0000009387967452312)
+ 0.0000001815600541022
* :Temperature +
0.0000000218633389171 *
:Temperature ^ 2, Quadratic Model

Predicted 95% CI=
(-27.8898211558579)
+ 23.9294245426114 *
Exp(0.0376760939674008
* :Temperature), 3 Parameter
Exponential Model

Predicted Expiry=
33.5848316003024 +
7328.12608635937 * Exp(-
0.196329985274204 *
:Temperature), 3 Parameter
Exponential Model

Predicted Accelaration
Rate= 25.9675472550865 +
1008.32460629621 * Exp(-
0.116629176337002 * :Temperature),
3 Parameter Exponential Model

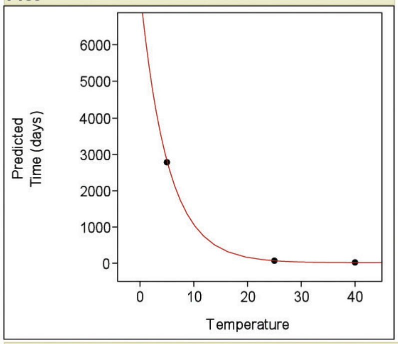
6. Check the model to make sure it matches the actual data. Correct any modeling errors.
7. Create a profiler (**Figure 7**) from the equation. This can be done using a modern statistical package such as SAS/JMP.
8. Predict expiry at any temperature using the profiler. A temperature of 4 °C was not part of the study design; however, it now can be modeled using the prediction profiler.
9. 95% CIs are often not helpful in estimation of long-term stability due to the limited sample size.

Figure 6: Generalized temperature models.

Fit Curve — Model Comparison

Model	AICc	BIC	SSE	MSE	RMSE	R-Square
Exponential 3P	.	-95.41365	6.251e-16	.	.	1

Plot



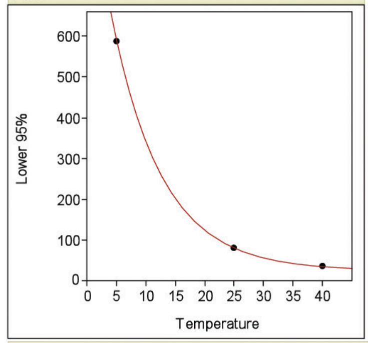
Exponential 3P — Parameter Estimates

Parameter	Estimate	Std Error	Lower 95%	Upper 95%
Asymptote	33.584832	.	.	.
Scale	7328.1261	.	.	.
Growth Rate	-0.19633	.	.	.

Fit Curve — Model Comparison

Model	AICc	BIC	SSE	MSE	RMSE	R-Square
Exponential 3P	.	-74.64316	6.35e-13	.	.	1

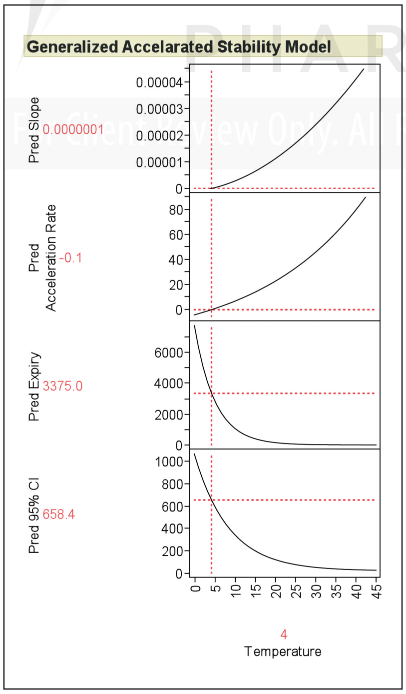
Plot



Exponential 3P — Parameter Estimates

Parameter	Estimate	Std Error	Lower 95%	Upper 95%
Asymptote	25.967547	.	.	.
Scale	1008.3246	.	.	.
Growth Rate	-0.116629	.	.	.

Figure 7: Generalized accelerated stability profiler.



The sample size directly impacts the 95% CI but not the slope as much. Expiry based on the slope is typically the primary focus.

In this example it is estimated at 4 °C the product will be stable for 3375 days or 9.2 years.

10. Finally, long-term stability evaluation at nominal storage conditions will be used to confirm the early model prediction and will provide an independent secondary determination of stability and changes in dissolution. Understanding rates of degradation should factor into shelf life and release specification limits (6).

SUMMARY

Reliable accelerated stability modeling and estimation has long been a problem in a variety of process and product modeling and prediction situations. The novel procedure discussed in this paper for the characterization of stability performance provides a clear, statistically defendable method for determining accelerated stability. Four primary tools are used in the generation of the analysis: design of experiments for the design of the study, ANCOVA model fitting, linear and non-linear model fitting of the coefficients, and profilers to integrate the equation and improve visualization and prediction. Long-term verification of accelerated conditions should always follow early determinations of expiry, acceleration rates and rates of degradation.

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