APPLICATION NOTE

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Accelerated Stability Assessment with Luminata

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Drug molecules slowly degrade over time depending on the storage environment's temperature, humidity, and light. For patients, these stability issues can lead to a loss of medicinal potency or increased side effects. Pharmaceutical development scientists thoroughly assess drug substances and drug products to ensure there are no stability concerns.

However, using only experimental methods to test drug stability is impractical, which has led researchers to develop computational approaches to address this problem. Chemical processes such as degradation follow mathematical rules, allowing scientists to predict the degradation rates under a range of conditions. This method is known as the Accelerated Stability Assessment Program (ASAP).

Unfortunately, many of the tools used to perform accelerated stability analysis do not integrate with analytical and chemical software. Researchers must manually transcribe data and manage files, which is inefficient and tedious. This article explores the fundamentals of accelerated stability calculations and how Luminata can be used to simplify ASAP assessments.

Introduction to Accelerated Predictive Stability

Luminata's ASAP workflow is based on an Accelerated Predictive Stability approach. It uses a linear regression analysis to predict the degradation of drug products in their packaging based on temperature and relative humidity. Degradation follows a modified Arrhenius equation:

$$\ln(k) = \ln(A) + \frac{-E_a}{RT} + B \cdot RH$$

Where:

k is the reaction rate
A is the collision factor
E_a is the activation energy
R is the gas constant
T is the temperature
B is the humidity sensitivity factor
RH is the relative humidity

To determine the rate of degradation, scientists run experiments at a range of temperatures and levels of humidity. Concentrations of degradants are typically assessed through chromatography data, where the area of product and degradant peaks are compared over multiple time points. This information can be used to compute the k, A, E_a, and B rate constants, which can then be generalized over a range of conditions.

In many cases, more than one degradant is being produced simultaneously or certain degradants are consumed in secondary degradation reactions. Each chemical reaction follows its own kinetics, meaning rate constants for each degradative process must be calculated separately. Together, these equations can be combined to act as a "digital twin" of the drug, allowing chemists to model the level of each degradant over time. This can then be cross-referenced with toxicity data to assess the likelihood of adverse effects for patients.

Challenges in Accelerated Stability Assessment

While the accelerated stability assessment calculations are clear in theory, there are several practical obstacles to completing these assessments, including:

- Processing the analytical data to determine the degradant levels for each set of conditions
- Calculating the reaction rate variables based on the analytical results
- Visualizing results and cross-referencing predicted degradation levels with toxicological information

These steps can require considerable time and effort, especially when teams lack the data management tools to consolidate the relevant data. Luminata includes features that address each of these challenges.

Accelerating Analytical Data Processing

Processing chromatograms to determine the level of each degradant is time-consuming, and error prone. Using Luminata, scientists can connect chromatography data from their degradation experiments to the stages of a process map. Luminata then calculates the level of each degradant for each set of conditions.

It is worth noting that users do not need to have elucidated structures when completing this assessment, as shown in Figure 1. Degradation rates can be calculated without any structural information. Researchers often use relative retention time (RRT) values during stability research, especially in the early stages of a project. As work progresses, structures can be populated.

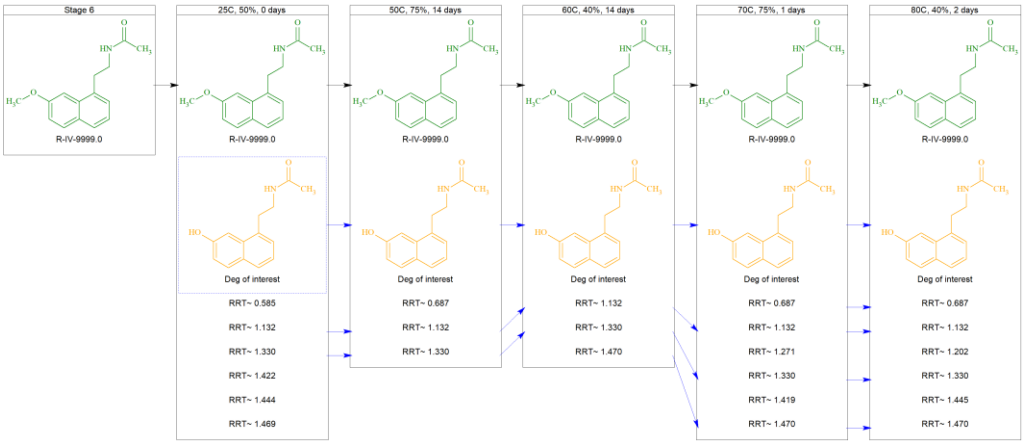

Figure 1. Example degradation map for Agomelatine. RRT values are used for unknown structures; these can be added as development progresses. Structures are not required to perform predicted stability calculations.

Simplified Stability Calculations

As stability data is added to Luminata, users also include each experiment's temperature, relative humidity, and time information. This information is used to calculate the modified Arrhenius equation parameters A, E_a, and B, which are necessary for accelerated stability prediction.

Luminata also includes R^2 and Q^2 values, which quantitatively assess how well the experimental data fits the model. These are useful checks to ensure the results are consistent and will help users identify data input or experimental errors.

Accelerated Stability Assessment Regression: Record ID: 8143 from Project "Agomelatine" and Process "APS"

Data

Amount Source: 220 nm Entity or Compound: Deg of interest

Use Time = 0 point: Do not use

Regression Data | Arrhenius Data

Stage Name	Temp (C)	Humidity (%)	Time (days)	Peak Area	Predicted Peak ...
25C, 50%, 0 days	25	50	0	0.0392	
50C, 75%, 14 days	50	75	14	0.4287	0.4197
60C, 40%, 14 days	60	40	14	0.7183	0.7346
70C, 75%, 1 days	70	75	1	0.1969	0.2011
80C, 40%, 2 days	80	40	2	0.6453	0.631

Regression Data | Arrhenius Data

lnA	28.2473	±	0.7046	
E_a	87.7395	±	2.0682	kJ/mol
B	1.2014e-2	±	1.3928e-3	
Experimental vs Predicted:				
Corr. Coeff	0.9983			
Determ. Coeff	0.9967			
Intercept	-3.1985e-3			
Slope	1.005			
Model Quality:				
R^2	0.9966			
Q^2	0.9488			

Figure 2. *Arrhenius variables calculated from experimental data. Includes R^2 and Q^2 values to assess model fit.*

Modelling and Visualization

Once these steps are completed, users can model the stability of the drug substance or product being analyzed. Luminata also includes visualization tools, which help users interpret the results of their accelerated stability analysis, allowing scientists to:

- → Compare the rates at which different degradants are formed
- → Forecast the degradant profile at a specified stability study time point
- → Create a PDF report that summarizes the results of the accelerated stability assessment

By performing their chromatographic analysis, stability calculations, and predictive modeling in one place, users will save considerable time. This also limits the need to carry out complete experimental stability tests, which are resource intensive.

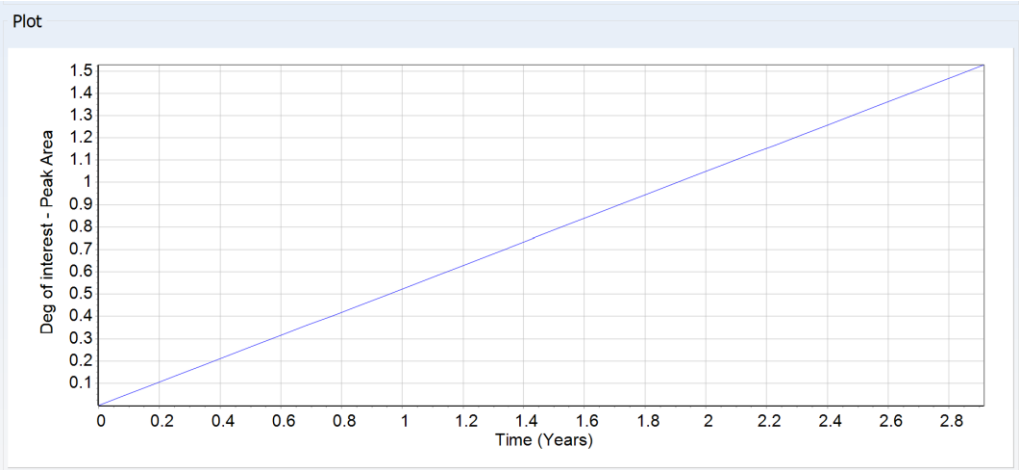

Figure 3. Predicted levels of degradant formation over a three-year time span.

Luminata—Stability Study Decision Support

As development continues, the RRT values used in the original degradant map can be replaced with structures. Luminata offers a rich set of structure elucidation tools to help with this process. These structures can then be linked to physiochemical properties, reference data, toxicity predictions, and more.

Luminata offers many other features designed to streamline stability research. This includes importing predicted stability maps from third-party software (e.g., Lhasa Zeneth), forced degradation study templating tools, and a dynamic project map for managing research teams. Users have a complete dashboard to assess stability for all stages of pharmaceutical development, leading to better productivity and better medicines.

Learn more about Luminata's tools for stability studies.