Accelerated Stability Analysis Platform: Extending the art of model generation, evaluation and visualisation

Martin Owen, Rachel Orr, Neil Hodnett, Don Clancy. GlaxoSmithKline
David Burnham (Pega Analytics)

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“Understanding and controlling the stability of medicines is key to the safety of the patient”

The long-term stability of pharmaceutical formulations is traditionally evaluated by exposing the product to a variety of standardized conditions for up to five years. This paper looks at ways to accelerate the generation of process understanding in a couple of weeks, to enable us to make earlier key decisions about stability. Models are used to make extrapolated “what-if scenario predictions” at different temperature, humidity and packaging conditions and these extrapolated predictions can be verified by long term data as and when required.

Current established practice: Long-term stability studies

Formulation studies involve developing a preparation of the drug which is both stable and acceptable to the patient. For example, with orally taken drugs, this usually involves incorporating the active drug substance into a tablet or a capsule. A tablet contains a variety of other substances apart from the drug itself, and stability studies have to be carried out to ensure that the drug is compatible with these other substances.
We need to provide evidence on how the quality of the drug substance or product varies with time under the influence of a variety of factors such as temperature, humidity and light.

These studies enable the link between storage conditions and shelf-lives to be established. The extended storage conditions are designed to represent different climates across the world.

To control the impact of humidity, medicines are commonly packaged in a bottle or blister pack, and sometimes with desiccant. Over time moisture permeates the packaging which can cause instability in the active drug substance resulting in increased impurity levels and decreased efficacy. The container systems can be made from a variety of materials including glass, plastic, and metallic foil.

**The need for accelerated Stability studies**

In practice we need early evidence of stability when developing drugs rather than having to wait for years before the long term study reads out.

For example if the drug proves unstable, it will invalidate the results from clinical trials since it would be impossible to know what the administered dose actually was.
Accelerated stability studies enable us obtain an earlier read out, by exposing a drug product to more extreme storage conditions (temperature and humidity) for short periods, typically 14 days, simulating what would happen over longer periods of shelf life.

This early detection of potential instability (weeks instead of years) allows us to take action to mitigate or control risk.

We can make early science and risk-based data-derived decisions on route selections, formulation choices, assess changes to starting material manufacturers and trouble shoot stability issues. We do this by using extrapolated models to predict the shelf life of drug substances, drug products, intermediates and starting materials.

We can assess options for mitigating risk e.g. by modeling different packaging and desiccant choices to control stability. We can also reduce packaging and carbon footprint costs by minimising packaging where appropriate.
The accelerated study concept has had significant exposure to regulatory agencies across the globe. The concept is considered to be an improvement on current working practices for assigning retest periods. At this stage we do not suggest ASAP studies are a replacement for long term studies, rather that they provide an early indicator as to the likely risk of drug instability, allowing a way of evaluating control strategy options and prioritising the most appropriate long term stability studies to perform.

We do have examples where extrapolated accelerated study predictions are in very close agreement with long term models.
The Accelerated Stability (ASAP) workflow

| Design Set-up | • Define the Problem:  
|              | • Design experimental protocol  
|              | • Perform the experiments  
|              | • Gather and collate the data |
| Model        | • Fit kinetic models  
|              | • Develop a long term humidity model  
|              | • Extrapolate kinetic models |
| Take action  | • Communicate impact  
|              | • Make data-derived decisions |
| Review       | • Verify the models with long term data  
|              | • Review updated models |
| Organisational learning | • Build a portfolio of examples  
|              | • Review portfolio  
|              | • Adapt and improve |

Who is involved?

At GSK there are three types of users involved the ASAP process.

- The expert modellers support an ASAP lead user group.
- The ASAP user group provide the stability study service for project teams and senior decision makers in Development and Manufacture.
- The project teams and senior decision makers in Development and Manufacture are responsible for ensuring drug product meets quality objectives.

The approximate size of the groups is as follows:
The key to increasing the uptake of ASAP is recognising that complex mathematics underpin the ASAP workflow. We need to combine kinetic models and humidity models to create a combined model with which we can make predictions. We then need a dashboard or interface that is easy to use by non–experts.

**Stability protocol: practical experimentation**

Before we focus on the dashboard, we will first take a look how we actually perform the study in the laboratory as this helps to explain the protocol and how and when the data is collected.

The temperature is controlled by using ovens set at different temperatures.

The humidity is controlled using salts.
Samples are stored in chambers. Typically we use up to six chambers.

Each chamber contains a data logger to record the actual temperature and relative humidity every twenty minutes.

During different time intervals samples are withdrawn and analysed by HPLC for impurity content. Different impurities have different retention times and the amounts of each impurity can be determined by the area of each peak.
The ASAP Dashboard Application

The application handles the associated data-handling workflows, the complexity of the modeling and delivers a capability for engaging multi-disciplinary problems solvers. All information is presented visually and interactively in a dashboard format. This enables decision-makers, who may not themselves build the models, to access advanced analytical and statistical methods, explore what-if scenarios in real-time and evaluate that the quality of the model is fit for purpose.

Expert modeller requirements

- Automated model building to remove the burden of repetitive key strokes and free up experts to work on challenging problems
- The ability to override automated models and insert manually produced models
- Clear and transparent line of sight between data and model production so that if required, data can be checked and modeling assumptions can be tested
- The flexibility to refine and extend the modeling capability, visualisation of uncertainty, and packaging/desiccant options
- Rapid access to previously constructed models
- Access to the source code and look up tables

ASAP Lead User Requirements

- Connectivity to data storage systems (currently excel)
- Easy to use interface and intuitive workflow
- Standardised procedures in design set-up and data collection to maximise efficiency and enable automation of data transfer
- Capability to explore data to visualise overall risk (overview) and assess importance of specific impurities (zoom and filter)
- Access to the data extract table to (details on demand) to prioritise responses and exclude data that is inappropriate for modeling
- Easy model retrieval

Project team members and senior managers

- Easy to assimilate information
- Easy to interrogate “what if scenarios”
- Quick visualisation updates in “real time” enabling live use in project meetings
- Easy to operate interface to enable communication of control strategy options
- Uncluttered display with technical detail available on need to know basis
- Helps consensus building in scientific and risk-based data-derived decision making

Requirements for choice of software package to build a dashboard

Historically excel was used to manually produce ASAP models. Alternative data analytic packages were evaluated and one with the following required capabilities was selected
Data handling capability (e.g. split and stack functionality)
Interface with data storage solutions
Flexible and rapid data visualisation
Linear and non-linear modeling
Dynamic, interactive model/visualisation
Capability to enable knowledge capture, retention and retrieval
Scripting to provide workflow type platform
Open source code

Data Analytics Workflow from the perspective of the modeller

The Data Analytics Workflow is as follows:

- Build Storage Model
- Build Kinetic Models for Impurities
- Estimate Shelf Life for each impurity

The Storage Model

We need to generate mechanistic model that models the moisture permeation. The model needs to account for these effects:

- Permeation of moisture into a storage bottle
- Moisture equilibrium between headspace, desiccant, and tablet
- Desiccant and Tablet moisture absorption
- Rate equations for formation of impurities in presence of water

Typical Equilibrium Moisture Content of Tablets

A tablet “isotherm” is constructed relating the percent moisture to the Relative Humidity of the chamber using Gravimetric Vapour Sorption (GVS) data. The tablet isotherm model is used to calculate percent moisture content at a given relative humidity. A similar isotherm
is developed for the desiccant. The equilibrium relative humidity is calculated for each moisture content in the storage bottle by solving a mass balance relating 4 equations and 4 unknowns (relative humidity, moisture in headspace, moisture in tablet, moisture in desiccant). The model calculates moisture permeation into the storage bottle over time corresponding with the plastic’s permeability, bottle surface area, and bottle wall thickness.

**Build Storage Model**

The storage model locates an equilibrium condition for the environment based on temperature, moisture and physical dimensions of the container. An iterative method is used to continually re-evaluate multiple equations that describe the physical environment, and in particular the moisture within the tablet and within the surrounding headspace. Iteration continues until an equilibrium condition is identified.

This yields the day-zero steady state conditions.

Taking account of water vapour pressure and the permeability of the barrier materials, the above iterative procedure can be repeated for each day over a two year period to take calculate the uptake of moisture into the tablet.

If a desiccant is included, the moisture fraction for the desiccant is also calculated.
The dashboard is used to visualise this information and to investigate different packaging options:

The kinetic model

Build Kinetic Models for Impurities

For each impurity a kinetic model is built based on the results of accelerated lifetime studies. These studies use extreme levels of temperature and humidity.

The generic form for these models is:

$$\text{Impurity} = K_1 e^{-\frac{K_2}{\text{temperature}}} \cdot (\text{Humidity})^{N_1} \cdot (\Delta \text{Time})^{N_2} + C$$

Kinetic modelling terms

$N_1$ **Humidity sensitivity term**

The Humidity term in the model could be relative humidity, or alternatively could be proportional to the vapor pressure of water:

- Relative humidity would indicate the kinetics are driven by liquid water, as material moisture content is proportional to relative humidity.
- Absolute humidity: Vapor pressure of water would indicate the kinetics are driven by moisture in the vapor phase.

$K_1$ **Arrhenius pre-exponential term**

$K_1$ is the frequency factor and relates to the activation energy for the degradation process

$K_2$ **Activation energy; temperature sensitivity**
**Asymptote** - For a decelerating model, the asymptote defines the maximum level of impurity that can be formed in the batch and may relate to the level of a precursor impurity present in the batch.

Estimates for the parameters are made using the JMP nonlinear platform.

There is no a priori way to know whether the impurity levels are driven by relative humidity (RH) or absolute humidity (AH). So two sets of models are built:

A set of heuristic rules are applied to the models to evaluate whether the parameter estimates are “scientifically reasonable”:

At this point the models are being used primary to assess whether relative humidity (RH) or absolute humidity (AH) is the driving mechanism. Once this has been established the goal is to find the simplest model consistent with the data. A model linear in time is constructed:
Further heuristics are applied to establish the suitability of the linear model. If the fit is acceptable a green traffic light is displayed. If not, an amber traffic light and a warning message are displayed.

The decision to choose a particular model is based on: (a) whether the impurity formation is linear with time, (b) is speeding up, or (c) slowing down with respect to time.
We now have a functional form that describes the level of impurity at a given time point for specified levels of temperature and humidity. It is important to realise that the humidity will be a function of the environment (storage conditions) and the packaging materials. Combining the moisture flux results from the storage model with the kinetic model yields a set of data that describes the time-evolution of impurity level within the tablet:

![Impurity Models - IMP Pro](image1)

The dashboard is used to visualise the development of impurities over time:

![Predicted Impurity Content](image2)
Confidence intervals are computed for the models, and the cross-over with specification limits results in an estimate for shelf life:
The Dashboard concept

This picture illustrates the main features of the ASAP Dashboard Application. The purpose of a dashboard is to bring together, in close proximity, the information required in order to make decisions.

Dashboard Workflow from the perspective of the end-user

Design set-up

Accelerated stability studies are designed in a way that effectively deconvolutes the effect of time and temperature. This feature helps identify a fit for purpose design with appropriate factor ranges and combinations.
The data from the HPLC systems and the data logger systems is combined into a simple standardised format excel table

<table>
<thead>
<tr>
<th>Name</th>
<th>Stab Study #</th>
<th>EE Ref.</th>
<th>Type</th>
<th>Batch ID</th>
<th>Analysis replicate</th>
<th>Temperature</th>
<th>Relative Humidity</th>
<th>Time</th>
<th>RRT 0.11</th>
<th>RRT 0.94</th>
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<td>Tablet</td>
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<td>27.3</td>
<td>2</td>
<td>0.0019</td>
<td></td>
<td></td>
</tr>
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<td>43.3</td>
<td>2</td>
<td>0.0903</td>
<td></td>
<td></td>
</tr>
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<td>50.2</td>
<td>27.3</td>
<td>5</td>
<td>0.0125</td>
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<td>Tablet</td>
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<td>49.7</td>
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<td>46.1</td>
<td>2</td>
<td>0.0000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This excel table is then imported into the data analytics package for a preliminary evaluation of the data. The overview gives an immediate sense of which where the greatest risk occurs.
The zoom and filter option allows us to perform a more rigorous inspection of the data, identify potential data outliers as a result of data entry/transcription errors or processing errors.

Once we are happy with the data and we know which impurities are appropriate to model, we can start to build the models for specific batches and impurities.

The dashboard interface

As you can imagine, generating and coupling these models can be very complex, which is why we have worked to develop a dashboard which automates the modelling “behind the scenes” to give a clean uncluttered interface for the decision makers. The end-user can vary parameters, evaluate risk and determine potential controls.
On the right hand side you can see an evaluation of risk. This shows the predicted shelf life or time to break specification for each attribute. This can help us determine where our risk lies and what we need to control.

The left hand side of the dashboard contains the parametric control. The graphs display the MVTR models and the drop down menus contain options for different packaging types.

Additional customisations are available in the control panel. Here we can specify the exact dimensions of our packaging to make the model most appropriate for our application. Any changes made on the control side of the dashboard are reflected in the degradation profile and risk analysis on the right.

It is then possible to add the long-term stability data as it becomes available and overlay it to verify the model or supersede it if necessary.

**Adding value**

**Case study I**

In this example one strength of a high strength product was already on the market with available long term stability data. An ASAP study was run. We can overlay the long term data with the ASAP model (see A). The central blue line shown is the prediction with 2 sided 95% confidence intervals shown within the shaded area. The black spots are the long term data points and, as can be seen, they overlay well with the prediction.

An ASAP study was run with a lower strength product to assess its viability and packaging changes that may be required to achieve a marketable shelf life.
The ASAP model of the lower strength product shows (B) the degradation rate is much higher and would not enable a marketable product. However, if we now select a desiccant for inside our pack (C) we see the risk reduce as the predicted shelf life extends for the 0.94 impurity. Note that bar charts below the models also show that the desiccant does not impact on the 0.11 impurity in the same way. This impurity is managed by controlling the initial water content of the tablet by prolonged drying time. This gives some idea of how that the control strategy required to manage different impurities can be challenging and the utility of a modeling approach.

(A) High strength product (no desiccant)       (B) Low strength product (no desiccant)       (C) Low strength product (with desiccant)

Case study II

A project about to be commercialised identified a stability issue with an unknown root cause. With a tight deadline for regulatory filing, the project team conducted an ASAP study with varying drug substance and excipients batches.

By utilising the "view all batches" option we can appreciate the impact of excipient sources. It materialised that it was the variation of excipient content in the batches that were causing the variations in the drug product degradation profile. It was also discovered that the reaction producing the impurity was self limiting, with all batches plateauing off before the specification. The control strategy in this case enabled us to select specific batches with acceptable excipient content going forwards in commercial manufacture.
What next?

The ASAP Dashboard Application has been developed very rapidly by building, testing, incorporating feedback from the modeling team and lead users. The application has progressed from a static mock-up of the user interface (v0.1), through to a working version with minimal capability (v1.2), through to a more robust and fully functioning version (v1.6).

Our intent is to continue to build in additional capability, such as non-linear modeling and look at the requirements for scaling this out into an “industrialised” version for use throughout the company. We will continue to build our portfolio of applications and refine the process and protocols as our experience grows.

![Diagram showing versions v0.1, v1.2, v1.6, and v2.0 over time: Nov ’13, Feb’14, July ’14, Dec ‘14]

Key Learnings for Dashboard Application Development

The most important element in the success in building this capability has been to understand the business requirements and understand the different needs of the people involved in the ASAP process (modelling experts, ASAP lead Users, drug product project team member and senior decision-makers).

The team members responsible for developing the application have diverse technical capabilities and team-styles. In particular, the team behaviour which is particularly helpful to make rapid progress is a cohesive, flexible, responsive and can-do attitude.

We had several options of software packages to explore and develop this capability. The one we chose had the required functionality, flexibility and ease of use to make progress very quickly.

Finally we caught the imagination of the organisation and individuals who have been prepared to do something different, take action and to add value.