Outline

- Opportunities
- Overview of ASAP
- Areas of Application
- ASAP Proposal to Regulators
- Summary
Opportunities

- Provide cost benefits and possible alternate methods for demonstrating product stability

- Ability to leverage ASAP to provide regulatory flexibility

- Facilitate the rapid assessment of out of specification (OOS) issues and continuous improvement

- Utilize the program to explore package model concepts. This will minimize explicit screening of packaging configuration for drug products.
Accelerated Stability Assessment Program (ASAP): Overview

- ASAP is a predictive tool that combines experimental data and Arrhenius-based modeling for rapid chemical stability assessment of drug products.

- Samples are placed in an open dish to allow the impact of temperature and %RH conditions to be modeled in approximately 2-4 weeks.

- A typical ASAP study involves 6-8 storage conditions with temperatures ranging from 50°C to 80°C, and relative humidity from 10%RH to 75%RH.

- The resulting degradation and potency loss which targets the specification limit is modeled using the humidity corrected Arrhenius equation to predict shelf life at milder conditions.

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

- ASAP studies are iterative to establish a product specific model.
### ASAP Screening Protocol

<table>
<thead>
<tr>
<th>Protocol</th>
<th>T (°C)</th>
<th>%RH</th>
<th>Days 1st Pull</th>
<th>Days 2nd Pull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Product Stability</td>
<td>50</td>
<td>75</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td>(Solid Oral Dosage Form)</td>
<td>60</td>
<td>10</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>40</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>10</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>75</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>40</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>

- Six to eight-point protocol is normally used to effectively model the influence of temperature and relative humidity.
- Second study is required in most cases using adjusted exposure times at each condition in order to achieve degradation at the specification limits.
Various packaging dictates the product stability behavior and ASAP can be used to support packaging design concept.

The sorption-desorption moisture transfer model (SDMT) is to predict drug product stability within various packaging configuration.

Implicit Package screening depends on:
- External Temperature and %RH
- Moisture permeability (Moisture Vapor Transmission Rate)
- Moisture isotherms of internal materials (tablets, desiccants)
- The tablet/capsule count
- Water Activity
  - Water activity is a critical factor that dictates physical and chemical changes
  - The importance of water activity in understanding and improving drug stability has been supported by the ASAP program

MVTR can be established for most bottles, blisters

Moisture isotherms depend mostly on excipients: standard database established.
Areas of Applications

- Formulation Development: API-Excipient Compatibility Studies
- Coating screenings
- API synthetic route optimization (e.g. solvents, particle size, form)
- Process changes (e.g. dry vs wet granulation, scale differences, direct compression vs granulation, batch vs continuous)
- Raw material changes (e.g. different vendors, grades)
- Developing Packaging Design Concepts (e.g. Pvc to Foil-foil blisters, bottles w/w-o desiccant)
- Support the Optimization of Manufacturing Conditions
- Tech Transfer Support
- Support Root Cause Investigative Studies
Case Study # 1: Accupril Tablet Stability Issues

- ASAP provided support in investigating the stability failure associated with the drug product.

- Failure to meet specification under Zone IV Conditions were observed

- The excipient Magnesium Carbonate was identified as the possible contributing factor to the out of specification issues

- Leveraged the ASAP model to examine the impact Magnesium Carbonate has on controlling the product stability behavior.
The degradant Quiniprilat has a relatively higher rate of formation which limits the shelf life of Accupril Tablets; degradant pathway for the main degradant is ester hydrolysis.

Quiniprilat results generated at various ASAP conditions were fitted into an ASAP model and used to extrapolate shelf life estimates.

Shelf life estimates at ICH stability conditions were determined for a lot packaged in foil-foil blister packs.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Exposure Time (Days)</th>
<th>%Degradant (Quiniprilat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5C-5%RH</td>
<td>-</td>
<td>0.40</td>
</tr>
<tr>
<td>40C-75%RH</td>
<td>4.99</td>
<td>3.73</td>
</tr>
<tr>
<td>50C-75%RH</td>
<td>1.02</td>
<td>3.34</td>
</tr>
<tr>
<td>60C-5% RH</td>
<td>13.79</td>
<td>1.14</td>
</tr>
<tr>
<td>60C-40%RH</td>
<td>3.13</td>
<td>3.21</td>
</tr>
<tr>
<td>70C-5%RH</td>
<td>13.79</td>
<td>2.85</td>
</tr>
<tr>
<td>80C-28%RH</td>
<td>0.45</td>
<td>3.83</td>
</tr>
</tbody>
</table>
Available real time stability data was provided for sample lot packaged in foil-foil blister pack under Zone II conditions.

A comparison profile established between the real time data and predictions demonstrated good agreement.
Comparison Profile:
ASAP vs. Real Time Data (30C/75%RH)

Real Time Data vs. ASAP Predictions:
Degradant: PD109548
(Condition 30C/75%RH)

- Blue: Shelf Life Estimate (median)-Commercial Lot
- Orange: Real Time Data
- Red: Confidence Limit (95%)
- Green: Confidence limits (Real Time Data)

% PD109548 vs. Time (Years)
Batches manufactured using medium heavy grade MgCO$_3$ required significantly less water to reach the granulation endpoint.

ASAP studies performed on various formulations demonstrated instabilities associated with the batches using medium heavy grade MgCO$_3$. 
ASAP studies were performed on the in-process samples for each batch. An increase in the amount of water added was directly related to the shelf life estimate of the samples.
Case Study # 2: Amlodipine Besylate Tablets (5 mg) ASAP Study

- ASAP provided support in extrapolating shelf life estimates for Amlodipine Besylate tablets (5 mg)

- This study was a part of an ongoing effort to gain an improved understanding of the stability issues associated with the product

- Tablets were placed in an “open dish” environment at the assigned ASAP conditions.
# Amlodipine Besylate Tablets (5 mg) ASAP Study

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Amlodipine Besylate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Software</td>
<td>ASAP prime Version 3.01</td>
</tr>
<tr>
<td>External Conditions</td>
<td>30C/65%RH / 30C/75%RH</td>
</tr>
<tr>
<td>Specification Limits</td>
<td>0.5%</td>
</tr>
<tr>
<td>Packaging Configuration</td>
<td>PVdC Blister Packaging</td>
</tr>
<tr>
<td>MVTR (mg/cavity/day)</td>
<td>0.0669 (30C/65%RH)</td>
</tr>
<tr>
<td></td>
<td>0.0769 (30C/75%RH)</td>
</tr>
<tr>
<td>Initial %RH (Water Activity)</td>
<td>33% RH</td>
</tr>
<tr>
<td>Weight per tablet (mg)</td>
<td>200 mg</td>
</tr>
<tr>
<td>GAB Parameters derived from moisture isotherm</td>
<td></td>
</tr>
<tr>
<td>Wm</td>
<td>2.573</td>
</tr>
<tr>
<td>C, GAB</td>
<td>12.65</td>
</tr>
<tr>
<td>K GAB</td>
<td>0.780</td>
</tr>
</tbody>
</table>
A comparison profile established between the real time data and ASAP predictions under Zone IVa demonstrated consistency.

Predictions are based on the drug product packaging in PVdC blister film pack.
The “B” value for the target degradant is 0.05
Indicates the drug product’s propensity to be influenced by changes in %RH
Degradant formation via oxidative reaction which is catalyzed by H⁺ and OH⁺ ions
ASAP model was used to evaluate the long term stability performance of the drug product in Aclar and foil-foil blister films.
ASAP Predictions:
Packaging Design Concept

- Significant decrease was observed in the formation of the OOS degradant in the foil-foil blister packs.

- The OOS degradant maintained the acceptable level (0.5 %) after three years under Zone IVa conditions based on foil-foil packaging.
Case Study # 3: Zoloft Tablets – Process Change

- Blend used in Zoloft Tablet formulation was changed from a wet granulation to a dry granulation process

- Risk Mitigation: Investigate the potential for increased degradation as a result of change to the granulation process

- ASAP was employed to provide chemical assessment of the degradant/impurity profile for the product

- The low levels (within specification % at 30C/75%RH) of the degradation products will have no implications on the shelf life of the re-processed drug product
Zoloft Tablets – Predicted Impurity Profile for New Process

Degradant: Impurity A
(Condition: 30°C/75%RH)

- Shelf Life Estimate (median) - Impurity A
- Confidence Limit (95%)
- Spec Limit (0.5%)

Degradant: Impurity B
(Condition: 30°C/75%RH)

- Shelf Life Estimate (median) - Impurity A
- Confidence Limit (95%)
- Spec Limit (0.5%)
Proposing ASAP to Regulators as an alternative to traditional stability commitments

Enablers of innovative approaches

- ICH Q1A (R2): Alternative approaches can be used when there are scientifically justifiable reasons”
- WHO Stability Guideline: “However alternative approaches can be used when they are scientifically justified”
- ICH Guidances Q8, Q9 on Pharmaceutical Development and Risk Management
For registration filings, Pfizer will validate the model predictions against real time data for a specified drug product.

Comparison profile between the real time data and extrapolated shelf life estimates demonstrated similarities.
Proposed Package Change for Lipitor tablets: Removal of desiccants from bottle configurations

- An evaluation of the packaging w/o desiccant demonstrated a slight increase in degradation for the main degradant PD140728
- Packaging w/o desiccants *still* supports the approved shelf life of three years (Spec limit = 0.5%).
Bridging Science and Regulations

- Increased understanding of chemical degradation mechanisms (faster access to degradation information; specification rationales; key to mechanistic understanding of degradation issues)

- During Development
  - Use ASAP to predict stability for changes in:
    - Formulations/processes
    - Synthetic routes
    - Packaging Development

- At Registration
  - Use ASAP as supportive data or as an alternative to traditional stability studies to minimize stability commitments

- Post-Approval
  - Reduction of packaging studies needed to support product registration
  - Replace annual commitment with ASAP commitment.
Summary

- ASAP:
  - Enables the rapid chemical assessment and expiry date setting of pharmaceutical products
  - Supports the development of optimum packaging solutions for products, saving time and cost
  - Enhance scientific understanding of drug products
  - Lower risk for conventional stability failures

- Engaging and educating the regulatory agencies on the benefits of the program in supporting post-approval changes
  - Replace/supplement traditional stability studies.