Teaching Old Drugs New Tricks: Applications of ASAPprime in OTC Product Development

Jonathan E. Clark
The Procter and Gamble Company
SoS 9/26/16
• Overview of OTC Development

• Monograph Stability Design Strategy with ASAPprime

• MSR (Multi-Symptom Relief) Development Case Study

• Conclusions
Overview: Over the Counter (OTC) Drugs

Over-the-counter medicines provide $102 billion in value to the U.S. healthcare system annually.

$77B from clinical office visit savings
Doctor's appointments and diagnostics avoided

$102B
$25B

$25B in drug savings
Less expensive OTC medicines vs Rx


Every dollar spent by consumers on over-the-counter medicines saves the U.S. healthcare system $6–7 dollars.


http://www.chpa.org/MarketStats.aspx
Overview: OTC Development

Monograph Products

Differentiation through consumer understanding and novel product experience (new excipients)

New Filing (IND) Products

New Product Forms

Extended/Delayed Release

New API Combinations
Overview: Challenges in OTC

- OTC Monograph Modernization: ICH Q3B(R2)

### Attachment 1: Thresholds for Degradation Products in New Drug Products

#### Reporting Thresholds

<table>
<thead>
<tr>
<th>Maximum Daily Dose</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 1 ) g</td>
<td>0.1%</td>
</tr>
<tr>
<td>&gt; 1 g</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

#### Identification Thresholds

<table>
<thead>
<tr>
<th>Maximum Daily Dose</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 mg</td>
<td>1.0% or 5 μg TDI, whichever is lower</td>
</tr>
<tr>
<td>1 mg - 10 mg</td>
<td>0.5% or 20 μg TDI, whichever is lower</td>
</tr>
<tr>
<td>&gt; 10 mg - 2 g</td>
<td>0.2% or 2 mg TDI, whichever is lower</td>
</tr>
<tr>
<td>&gt; 2 g</td>
<td>0.10%</td>
</tr>
</tbody>
</table>

#### Qualification Thresholds

<table>
<thead>
<tr>
<th>Maximum Daily Dose</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 mg</td>
<td>1.0% or 50 μg TDI, whichever is lower</td>
</tr>
<tr>
<td>10 mg - 100 mg</td>
<td>0.5% or 200 μg TDI, whichever is lower</td>
</tr>
<tr>
<td>&gt; 100 mg - 2 g</td>
<td>0.2% or 3 mg TDI, whichever is lower</td>
</tr>
<tr>
<td>&gt; 2 g</td>
<td>0.15%</td>
</tr>
</tbody>
</table>
Overview: Challenges in OTC

Multi-Active Formulations

API 1
20 mg/dose

API 2
5 mg/dose

API 3
200 mg/dose
Overview: Challenges in OTC
Overview: OTC Degradation

- **Our Approach**

  What’s possible?

  What’s likely?

  What’s real?

  "Potential" Degradation Products (Combining All Stress Testing Results)

  "Actual" Degradation Products (Accel. / Long-Term RT Stability)

  "Actual" Degradation Products in final packaging / formulation / storage conditions

  “Knowledge” Space

  “Design” Space

  “Control” Space
• Overview of OTC Development

• Monograph Stability Design Strategy with ASAP \textit{prime}

• MSR (Multi-Symptom Relief) Development Case Study

• Conclusions
Holistic Stability Design Strategy

Commercial Concepts → Market Product

6-12 months
Holistic Stability Design Strategy
Stability Strategy Case Study: Monograph

- Flavor upgrade for Phenylephrine containing liquid product
Stability Strategy Case Study: Monograph

- Power and speed of ASAP\textit{prime}
Overview of OTC Development

Monograph Stability Design Strategy with ASAPprime

MSR (Multi-Symptom Relief) Development Case Study

Conclusions
Case Study: MSR New Drug Product

- **Product Concept:**
  - (IND/NDA filing) mixture of Naproxen (NAP), Dextromethorphan (DEX) and Pseudoephedrine (PSE) in 12 hour, extended release, bilayer tablet
  - During process scale up for prototypes and preparation for a clinical study, PSE was observed to be off-target high by 5-15%
  - An extraneous peak ~5% of parent DEX was also observed

Fig. 1: Overlay of high and on-target granulations and UV Spectra of API peak. Peak purity match of 993.
Case Study: MSR New Drug Product

- **Process Included:**

  - Dry blending
  - Wet granulation
  - Fluid Bed Drying
  - Tableting
Case Study: MSR New Drug Product

- The witch hunt

Original Conditions
- Restek Raptor C18 SPP Column, 0.1% TFA/MeCN

Alternate Selectivity for ID
- Agilent SB Phenyl Column, 0.1% TFA/MeCN

Optimized HPLC Conditions
- Waters T3 Column, 0.5% Ammonium Acetate/MeCN
Case Study: MSR New Drug Product

- **Identification**
  - Peaks were isolated via 1st dimension separation and fractionation
  - 2nd Dimension of HPLC was performed prior to analysis on a Thermo Exactive Mass Spectrometer
  - The HCD fragment spectrum confirmed a structural match with the proposed chemicals:

![Chemical Structures]

- DEX
- KETO DEX
- PSE
- Methcathinone

DEA Schedule 1 Controlled Substance
Case Study: MSR New Drug Product

Fig. 3: Presence of Metals in Formula Excipients (weighted by formula amounts)
Case Study: MSR New Drug Product

- **Materials characterization**
  - Are peroxides/metals observed in any raw materials?
  - Do the materials deliquesce?
  - What are the pH of API/excipient mixtures?

- **Results**
  - Raw materials not a major source of peroxides as received
  - Raw materials contribute reactive metals (i.e. Fe) at potential catalytic levels
  - Supplier specifications contain levels that can contribute to oxidation
  - Deliquescence occurs at lower RH for DEX/PSE mixture than for pure drug substance (55% vs 70%)
  - pH of API/HPMC mixtures range from 6-7.5
Case Study: MSR New Drug Product

- **Stability Assessment of DEX and PSE**
  - Are the API stable alone and in combination?

- **Results (via ASAPprime)**
  - Actives are stable individually and in combination
  - No degradation of either API observed at high temperature and high humidity
  - No inherent incompatibility between PSE and DEX
  - No degradation observed, even in samples undergoing deliquescence
Case Study: MSR New Drug Product

- **Excipient Compatibility Studies**
  - Do we need a formula change?

- **Results**
  - No inherent incompatibility between PSE/DEX and HPMC in the presence of high environmental moisture or spiked water at elevated temperatures

  Can’t break the molecules with ASAP
Case Study: MSR New Drug Product

- Analysis of In-Process Samples Isolated Unit Op of Formation

Fluid Bed Drying
Case Study: MSR New Drug Product

- Development of a Physical Model

Fluid Bed Dryer Simulator: conceptualization and execution
Case Study: MSR New Drug Product

• Development of a Physical Model

<table>
<thead>
<tr>
<th>Sample</th>
<th>Water</th>
<th>Fe$^{+3}$</th>
<th>Fe$^{+3}$ + H$_2$O$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSE</td>
<td>Not Detected</td>
<td>0.2%</td>
<td>18%</td>
</tr>
<tr>
<td>PSE/DEX</td>
<td>Not Detected</td>
<td>0.1%</td>
<td>3%</td>
</tr>
<tr>
<td>PSE/DEX/K100M</td>
<td>0.1%</td>
<td>0.4%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Degradation also observed in convection ovens, but much less in static ovens
Case Study: MSR New Drug Product

* Development of a Physical Model

<table>
<thead>
<tr>
<th>Factors Driving Degradation</th>
<th>Inhibitory Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air flow</td>
<td>Static environment</td>
</tr>
<tr>
<td>Heat</td>
<td></td>
</tr>
<tr>
<td>Mixing/Physical Contact</td>
<td></td>
</tr>
<tr>
<td>Catalytic metals</td>
<td>Chelator (EDTA)</td>
</tr>
<tr>
<td>Peroxides</td>
<td>Antioxidants</td>
</tr>
</tbody>
</table>
Conclusion

- **ASAPprime** is valuable upstream and downstream at P&G
- Oxidation and solid state chemistry is complicated
- HPLC matters, stability indication needs to be bulletproof (Peak Purity can be wrong)
• Allyn Kaufmann, P&G
• Samantha Donald, P&G
• Kylen Whitaker, P&G
• Jennifer Lewis, FreeThink
Thank you! Questions?

Touching lives, improving life. P&G™