Saxagliptin (Onglyza): A Case Study in Quality Risk Management

Stephen Liebowitz, Ph.D.
Group Director
Global Regulatory Sciences
Bristol-Myers Squibb
Objectives of this Presentation

To illustrate how Q10 was applied in the development of a new drug product and used in Production

To provide insight of knowledge management [1.6.1.] and quality risk management [1.6.2]
ICH Q10 (Scope 1.2) ... the product lifecycle included the following technical activities for new and existing products:

**Pharmaceutical Development**
- Formulation development
- Manufacturing process dev’t & scale-up

**Technology Transfer**

**Commercial Manufacturing**
ICH Q10 Knowledge Management (1.6.1)

• Product and process knowledge should be managed from development through the commercial life of a product...

• Knowledge management is a systemic approach to acquiring, analyzing, storing, and disseminating information related to products, mfg. processes, and components.
Knowledge Acquisition

• Defining the Product Profile
• Public domain literature, patent review
• API attributes and limitations
• Definition of the DP manufacturing process
• Ranging the manufacturing process
Knowledge Analysis

- Determining elements of intrinsic criticality, e.g. API attributes, process parameters, environmental conditions
- Risk analysis of the critical elements, e.g. FMEA, HACCP
- Defining a Control Strategy, e.g. integration of the process controls into facility QMS
Knowledge Storage

- Development reports
- E-notebooks
- E-network databases
- Manufacturing Orders
- SOPs, work instructions, best practices
Knowledge Dissemination

• Joint functional area meetings, deep dives
• Technology transfer- “go to the customer”
• On-site technology seminars
• Demonstration runs
KM and QRM - A Case Study
Saxagliptin

• Dipeptidyl peptidase IV inhibitor (DPP4) for Type II diabetes
• pKa = 7.2
• BCS Class III
Controlling Intramolecular Cyclization

Cyclization
- Occurs in solid and solution state
- Accelerates with commonly used excipients
- Accelerates when processed under wet & dry granulation
- Acidic environment stabilizes saxagliptin

Saxagliptin → Cyclic amidine

Pharmaceutical Quality System (ICH Q10) Conference
October 4–6, 2011 | Crystal Gateway Marriott | Arlington, Virginia
November 14–16, 2011 | Sheraton | Brussels, Belgium
DP Strategy- Film Coat Saxagliptin
The Critical DP Manufacturing Step

Placebo tablet

Coating contains drug
Analysis of Variables That May Impact the Coating Process

Various steps in coating
- Tablet movements in coater
  - Spraying of coating suspension on tablets
  - Drying of film coat on tablets
- Design of Coater and accessories
  - Pan load, pan rotation speed, baffle design
  - Spray rate, nozzle design, air to liquid ratio, nozzle to tablet bed distance, coating suspension homogeneity
  - Inlet temperature, air humidity, air volume

Analysis of Variables That May Impact the Coating Process
Comparison of different spray nozzles and spray patterns

Cone angle of (A) nozzle vs. (B) nozzle
Use of Raman to Monitor Coating
Process Optimization DOE was performed on Commercial Scale Equipment

Design: Saxagliptin Film Coated Tablets $2^{(5-1)}$ Fractional Factorial with 3 Center Points Design - 19 Runs

Actual Levels used for LOW(-1), CENTER(0), and HIGH(+1)

<table>
<thead>
<tr>
<th></th>
<th>API concentration</th>
<th>API/Polymer Ratio</th>
<th>Inlet Temperature °C</th>
<th>Total Spray Rate from 3 guns (g/min)</th>
<th>Atomizing Air+Pattern air per gun (SLPM)</th>
<th>Air Volume (CFM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW(-1)</td>
<td>2%</td>
<td>1:8</td>
<td>50.00</td>
<td>60.00</td>
<td>200.00</td>
<td>525.00</td>
</tr>
<tr>
<td>CENTER(0)</td>
<td>4%</td>
<td>1:4</td>
<td>52.50</td>
<td>81.00</td>
<td>250.00</td>
<td>560.00</td>
</tr>
<tr>
<td>HIGH(+1)</td>
<td>8%</td>
<td>1:1</td>
<td>55.00</td>
<td>105.00</td>
<td>300.00</td>
<td>600.00</td>
</tr>
</tbody>
</table>

A constant ratio of 1.5:1 was maintained between atomizing and pattern air for all runs.
Process Knowledge Acquired in Development and Transferred Forward to Production

- Key Quality Attributes identified after risk assessment
  - content uniformity
  - potency

- Design space established using fundamental process understanding, modeling and Design of Experiments (DOE)

- A predictive model for CU and potency created for the Coating Step
Data Analysis to Define a Control Strategy

Diagram:

- Drug Product
  - Critical Process Parameters
    - Critical Steps
  - Critical Quality Attributes
    - Potential Critical Process Parameters
    - Additional Control Points Beyond Standard Unit Operation Controls
## Quality Risk Analysis (ICH Q10 1.6.2)

<table>
<thead>
<tr>
<th>Event</th>
<th>A potential CPP because of impact and frequency</th>
</tr>
</thead>
</table>
| Severity | Consequence on Quality  
= HIGH Risk for potential CPP  
= LOW Risk for non CPP |
| Probability | = LOW Risk: operating range is well within the boundaries of proven range  
= MEDIUM Risk: operating close to the boundaries of proven range  
= HIGH Risk: operating close to the boundaries of proven range and the edge of failure |
| Overall Risk | Combination of severity and probability |
Communicating Risk Assessment

- **Severity (Consequence on Quality)**
  - Low Risk
  - High Risk

- **Probability (ability to control within the proven range)**
  - Low Risk
  - High Risk

- **Low Risk**
  - Potential CPP
  - Unlikely CPP

- **High Risk**
  - Likely CPP
  - Potential CPP
Production Process was Assessed for Criticality, Risk and Control

• A 5 Step Approach was taken
• Applicable for either drug substance or drug product
• When considering CPPs, determine what is critical and then how to control it
• Control of CPPs are additional to the standard level of controls
Drug Substance Process Controls

An Example of Process Parameter Risk Assessment using the 5 step approach
1. Lay out all the process parameters in each step

<table>
<thead>
<tr>
<th>Operation</th>
<th>Measurement</th>
<th>Parameter</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deprotection Reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Charge intermediate</td>
<td>Basis</td>
<td>moles</td>
</tr>
<tr>
<td>2</td>
<td>Charge solvent</td>
<td>Concentration of intermediate</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>Set agitation</td>
<td></td>
<td>rpm</td>
</tr>
<tr>
<td>4</td>
<td>Cool to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Charge reagent</td>
<td>Equivalents of sodium methoxide</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Heat to</td>
<td></td>
<td>deg C</td>
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<tr>
<td>7</td>
<td>Age</td>
<td>Temperature</td>
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<td>time</td>
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<td>hr</td>
</tr>
<tr>
<td></td>
<td>agitation</td>
<td>100</td>
<td>rpm</td>
</tr>
</tbody>
</table>
### 2. Compile Experimental conditions (target, proven, operating ranges) and establish Design Space

<table>
<thead>
<tr>
<th>Operation</th>
<th>Measurement</th>
<th>Parameter</th>
<th>Units</th>
<th>Min</th>
<th>Min</th>
<th>Min</th>
<th>Target</th>
<th>Max</th>
<th>Max</th>
<th>Max</th>
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<td></td>
<td>Charge solvent</td>
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<td>2.38</td>
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<td></td>
<td>Set agitation</td>
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<td>Cool to</td>
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<td>deg C</td>
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<td>10</td>
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<td>0.95</td>
<td>0.99</td>
<td>1</td>
<td>1.01</td>
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<td>Heat to</td>
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<td>27</td>
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</table>

#### Design Space

- **Expected Control Range for Factory**
- **Operating Range**
- **Propose Proven Range**

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### Propose Proven Range

<table>
<thead>
<tr>
<th>Operation</th>
<th>Measurement</th>
<th>Parameter</th>
<th>Units</th>
<th>Data ref for min proposed proven range</th>
<th>Data ref for max proposed proven range</th>
<th>Expected Control Range for Factory</th>
<th>Operating Range</th>
<th>Consequence of operating outside proven range low</th>
<th>Consequence of operating outside proven range high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degprotection Reaction</td>
<td>Charge Intermediate</td>
<td>Basis moles</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>Charge solvent</td>
<td>Concentration of intermediate</td>
<td>mL/g</td>
<td>63556-103</td>
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<td></td>
<td>2.2</td>
<td>2.7</td>
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<tr>
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<td>Set agitation</td>
<td>rpm</td>
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<td>50</td>
<td></td>
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<td></td>
<td>2.38</td>
<td>2.63</td>
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<td>Cool to</td>
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<td>10</td>
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<td>5</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
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<td>Equivalents of sodium methoxide</td>
<td>equiv</td>
<td>63556-066 to 077 1st DoE</td>
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<td></td>
<td></td>
<td>0.95</td>
<td>1.1</td>
</tr>
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<td>5</td>
<td>Heat to</td>
<td>deg C</td>
<td></td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td>0.95</td>
<td>1.05</td>
</tr>
<tr>
<td>6</td>
<td>Age</td>
<td>Temperature time</td>
<td>deg C</td>
<td>63556-102</td>
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<td>1</td>
<td>27</td>
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<td>7</td>
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<td>agitation</td>
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<td>10</td>
<td>23</td>
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</tbody>
</table>

### Diagram

- **Overlay the likely Production Control Capabilities**
- **Expected Control Range for Factory**
- **Operating Range**
- **Propose Proven Range**
- **Consequence of operating outside proven range low**
- **Consequence of operating outside proven range high**
4. Assess the risk of the process parameter on quality (CQA) to determine if it’s a likely CPP and consider needed controls

<table>
<thead>
<tr>
<th>Operation</th>
<th>Measurement</th>
<th>Parameter</th>
<th>Units</th>
<th>Expl Routine Factory</th>
<th>Capabilities</th>
<th>Expected Control Range for Factory</th>
<th>Operating Range</th>
<th>Consequence of operating outside proven range</th>
<th>Data ref for min proven range</th>
<th>Consequence of operating outside proven range</th>
<th>Impact on API CQA</th>
<th>In proven range outside expected control range</th>
<th>Risk of failing outside proven range?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Charge intermediate</td>
<td>Concentration of intermediate</td>
<td>2.5 mL/g</td>
<td>± 5%</td>
<td>Thick slurry</td>
<td>0.95 to 0.99</td>
<td>2.2</td>
<td>2.38</td>
<td>2.38</td>
<td>2.5</td>
<td>2.63</td>
<td>2.63</td>
<td>2.7</td>
<td>63556-19</td>
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<tr>
<td>2 Charge solvent</td>
<td>Concentration of intermediate</td>
<td>50 rpm</td>
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<td>3 Set agitation</td>
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</tr>
<tr>
<td>5 Charge reagent</td>
<td>Equivalents of sodium methoxide</td>
<td>1 equiv</td>
<td>± 5%</td>
<td></td>
<td></td>
<td>-0.95</td>
<td>0.95</td>
<td>0.99</td>
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<td>1.01</td>
<td>1.05</td>
<td>1.1</td>
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<td>7 Age Temperature</td>
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<td>8 Age agitation</td>
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</tbody>
</table>
5. Assess what additional work is needed to determine if parameter is characterized as a CPP

<table>
<thead>
<tr>
<th>Impact on API CQA</th>
<th>Is proven range outside expected control range</th>
<th>Risk of failing outside proven range?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low to medium, undercharge is corrected by IPC</td>
</tr>
<tr>
<td>Yes</td>
<td>marginal</td>
<td>Low to medium</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Low to medium</td>
</tr>
</tbody>
</table>
QRM in Manufacturing - Going Beyond Product Development

• QRM begins in Product Development and continues in Manufacturing as part its life-cycle management

• Knowledge gained during development is foundational to a process, and the manufacturing history builds on that knowledge base
QRM as Part of the Life-Cycle Management of a Product

- Process Changes- internal and external to the Design Space
- Input Material Changes
- Scale Changes
- Process Equipment Changes
- Site Changes
- Process Improvements
KM and QRM Summary

• KM and QRM begin in Product Development and continues through a product’s life cycle
• Understanding the product and its manufacturing process are needed to create an effective control strategy
• QRM is integral to executing an effective control strategy and maintaining the product
Acknowledgments

Toby Massa
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