Lean Six Sigma in Pharmaceutical QC Laboratories

Heather Longden
Topics

- Lean Six Sigma in the Pharmaceutical Industry
- Lean Six Sigma in the Analytical Laboratory
- Case Study – Improvement of Workflow and Documentation
- ELN for Lean Six Sigma Projects
- Summary
Lean Six Sigma in Pharmaceutical Manufacturing

Pharmaceutical Manufacturing

- Independent & isolated functions, divisions and geographical units
- Complex processes, many non-value added activities
- Focus on end product, not on process -> high rework rates
- Processes to be validated

Need to focus on reducing waste and variability
Manufacturing and QC Cycle Times

### Cycle Time Components

<table>
<thead>
<tr>
<th>Steps</th>
<th>In Process/Plant</th>
<th>In QA/QC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process/Unit Operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interruption of the process</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Securing of sample from process</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holding of sample in plant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documentation &amp; verification of sampling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transferring of samples to QC Lab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batching of samples in QC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparation of test samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual test-separation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual test-measurement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test data collection and processing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documentation &amp; verification of testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transferring results for review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decision regarding impact on process</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

©2011 Waters Corporation

Strategies to Increase Efficiency and Quality

**Lean**
Increasing efficiency by eliminating unnecessary steps within a process and reducing waste.

**Six Sigma**
Improve processes by eliminating defects and reducing variability.
Lean Management
- Eliminate non-value added activities (waste)
- Reduce complexity
- Improve flow

Improve Speed

Six Sigma
- Reduce variation
- Reduce defects
- Reduce Cost of Poor Quality (COPQ)

Improve Quality
Lean Labs?

Much more than just applying Spaghetti Diagrams...

Sample Preparation

Balance

Computer Station & Desk

Printer

Substances

Analyzers

Parts Bench

©2011 Waters Corporation
Roche – List of Selected Projects

<table>
<thead>
<tr>
<th>#</th>
<th>Project Name</th>
<th>Impact Area</th>
<th>#</th>
<th>Project Name</th>
<th>Impact Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Microbiology Sample Testing optimization</td>
<td>Laboratory/QM</td>
<td>13</td>
<td>Removal of Packaging Material</td>
<td>Production</td>
</tr>
<tr>
<td>2</td>
<td>Identity Testing of Raw Materials</td>
<td>Laboratory/QM</td>
<td>14</td>
<td>OEE - Reduction of Equipment Downtime, COPQ</td>
<td>Production</td>
</tr>
<tr>
<td>3</td>
<td>Metrology Optimization - HPLC Qualification</td>
<td>Laboratory/QM</td>
<td>15</td>
<td>Reduction of Equipment Downtime on M</td>
<td>Production</td>
</tr>
<tr>
<td>4</td>
<td>Equipment Rationalization - Balances &amp; Dissolution</td>
<td>Laboratory/QM</td>
<td>16</td>
<td>Pkg Line LL - Optimize Changeover &amp; Cleaning Process</td>
<td>Production</td>
</tr>
<tr>
<td>5</td>
<td>Release on Certificate of Analysis</td>
<td>Laboratory/QM</td>
<td>17</td>
<td>Raw Material and API Group Assessment</td>
<td>Production</td>
</tr>
<tr>
<td>6</td>
<td>Chemistry Lab testing optimization</td>
<td>Laboratory/QM</td>
<td>18</td>
<td>Cleaning Cycle Optimization - DFSS</td>
<td>Production</td>
</tr>
<tr>
<td>7</td>
<td>Implementation of Workload Sharing in Labs</td>
<td>Laboratory/QM</td>
<td>19</td>
<td>Bill Of Material Change and Implementation Process</td>
<td>Production</td>
</tr>
<tr>
<td>8</td>
<td>Floor Consolidation / Space Reduction</td>
<td>Laboratory/QM</td>
<td>20</td>
<td>Material Flow of Product T</td>
<td>Production</td>
</tr>
<tr>
<td>9</td>
<td>Efficient Compliance Report Process</td>
<td>Compliance</td>
<td>21</td>
<td>Batch Record Review</td>
<td>Production</td>
</tr>
<tr>
<td>10</td>
<td>Reduce Cycle time and Improve Quality of Report</td>
<td>Compliance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Streamline Compliance Report Data</td>
<td>Compliance</td>
<td>22</td>
<td>Cost Of Quality</td>
<td>Business Process</td>
</tr>
<tr>
<td>12</td>
<td>Gathering and Statistical Analysis</td>
<td>Compliance</td>
<td>23</td>
<td>Planning &amp; Scheduling Stability</td>
<td>Business Process</td>
</tr>
<tr>
<td>13</td>
<td>Reduction in Material Loss on X</td>
<td>Production</td>
<td>24</td>
<td>Weighing &amp; Dispensing Project</td>
<td>Production</td>
</tr>
</tbody>
</table>

Lean Six Sigma in the Analytical Lab

Pharmaceutical Manufacturing

- QC is the bottleneck
- Includes repetition
- Easy to be streamlined and improved by standardization
- High degree of reduction of manual steps and automation

“Lean Labs” will improve the overall productivity

Altria, Kevin D., Dufton, Ann M., Carleysmith, Stephen W., Learning from Lean Sigma, PharmTech, February 1 2009
Case Study -
Workflow and Documentation
Lean Six Sigma Project in Development at Eli Lilly and Company (global company / US HQ / approx. 38,000 employees / $23 B Rev)

Definition: Low efficiency due to duplication efforts and data loss due to manual data transfer processes.
Case Study – Measurement/Analysis and Improvement

- **Measurement/Analysis**
  - Lack of integration of lab workflows / informatics systems, non-value added steps and variability

- **Improvement**
  - Introduction of Electronic Laboratory Notebook for 300 scientists at different sites
Why Electronic?

- Increased Efficiency and Productivity
  ...thus additional project capacity
- Improved Quality of Documentation
  ...lessens burden for compliance and IP protection
- Cross Functional Area Searching
  ...retrieve or compile information and data
Situation Before Six Sigma Project
Define: Best Practices Lab Workflow (removal of variability)
Receive Samples (7 steps)

Enter Prep Info?

Yes

Enter Weights and/or Dilution Factors

No

Create Worklist?

Yes

Format Worklist for Transfer to Empower (26 steps)
## Projected LSS Value including Type IV

<table>
<thead>
<tr>
<th>Task/transfer</th>
<th># manual steps</th>
<th>Baseline cost$ – potential for Type II</th>
<th>Type IV ranking ◊</th>
</tr>
</thead>
<tbody>
<tr>
<td>LI MS → CDS</td>
<td>56*</td>
<td>~$11K</td>
<td>4</td>
</tr>
<tr>
<td>CDS → IL MS</td>
<td>12*</td>
<td>~$81K</td>
<td>5</td>
</tr>
<tr>
<td>Paper Notebook → CDS</td>
<td>Highly varied</td>
<td>~$540K</td>
<td>4</td>
</tr>
<tr>
<td>CDS → Paper Notebook</td>
<td>Highly varied</td>
<td>~$470K</td>
<td>1</td>
</tr>
<tr>
<td>LI MS → Paper Notebook</td>
<td>8*</td>
<td>~$46K</td>
<td>1</td>
</tr>
<tr>
<td>Paper Notebook → LI MS</td>
<td>40*</td>
<td>~$385K</td>
<td>4</td>
</tr>
<tr>
<td>SDMS → LI MS</td>
<td>63*</td>
<td>~$168K</td>
<td>4</td>
</tr>
<tr>
<td>CDS → SDMS**</td>
<td>42*</td>
<td>~$17K</td>
<td>2</td>
</tr>
</tbody>
</table>

** Logins
- eLN (3)*
- Empower (10)*
- IL MS (5)*
- SDMS (3)*
- Password re-entry due to Empower lockouts (6)*

<table>
<thead>
<tr>
<th>Logins</th>
<th># manual steps</th>
<th>Baseline cost$</th>
<th>Type IV ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>eLN (3)*</td>
<td></td>
<td>~$22K</td>
<td>2</td>
</tr>
<tr>
<td>Empower (10)*</td>
<td></td>
<td>~$73K</td>
<td></td>
</tr>
<tr>
<td>IL MS (5)*</td>
<td></td>
<td>~$28K</td>
<td></td>
</tr>
<tr>
<td>SDMS (3)*</td>
<td></td>
<td>~$33K</td>
<td></td>
</tr>
<tr>
<td>Password re-entry due to Empower lockouts (6)*</td>
<td></td>
<td>~$64K</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL** 242*  $2M  N/A

◊ Pain /Frustration Ranking;
  1 = lowest, 5 = highest,

** a report with multiple chromatograms for multiple aliquots is created in CDS and sent to SDMS. This SDMS report is attached to all affected aliquots in LIMS

* Includes some parallel processing
Critical to Change: What’s in it for Me?

- Can we...

  Can we... 

  ...minimize the impact of multiple systems?

  ...eliminate the scientist as the data transfer step?
Improve: the Desired Lab Workflow
Define: Best Practices Lab Workflow (removal of variability)

Begin Notebook Entries for Experimental Write-Up with Sample and Submission Info

NOTE: Documentation and transfer of information and references repetitive between ILIMS, Notebooks, logbooks is constant during the process (not shown for clarity purposes)
Meta Data

- Record or generate meta data *only once*
- Transfer data from systems to auto-populate
- Harmonize common fields (presence and usage)

### Meta Data

<table>
<thead>
<tr>
<th>What</th>
<th>Sources</th>
<th>Why</th>
</tr>
</thead>
<tbody>
<tr>
<td>- the identity, condition, and state of the samples</td>
<td>- User Supplied (Recorded)</td>
<td>- trace samples and link results (current analysis)</td>
</tr>
<tr>
<td>- preparation info needed to interpret results</td>
<td>- System generated</td>
<td>- find samples (future searching and data mining)</td>
</tr>
<tr>
<td>- the source of the samples (project, owner)</td>
<td></td>
<td>- create lab metrics (resource &amp; project management)</td>
</tr>
</tbody>
</table>

---

3/16/2011  
McCune_PittCon  
©2011 Waters Corporation
eLN – Vision Publisher

Serial Instruments (Balances, pH)

LIMS (Nautilus)

CDS (Empower)

SDMS (NuGenesis)
Measured LSS Improvements:
- Issuing, Tracking, Filming and Archival of Paper
- Searching – Meta Data, Text, Structures, Spectra
- Templates and Forms
- Cloning Experiments
- RS232 Integrations (balances, pH meters)
- LIMS/ELN/CDS Integration
- Create and Export Lists
- Transcription Errors

Measured productivity and ROI calculation:
- SDMS Integration
- Email
- Electronic Referencing
- Repetitive Searching
- eLogbook

Estimated Value
>$3M/year
What about the Labs?

- March 15, 2010 – mandated paperless for 3 labs
- June 30, 2010 – totally paperless in all labs

- June 30 – Steady State = 1150 Documents per month

- Cycle Time for Documents (Experiments) = ~11 days
- with best practices (templates, forms, balance integration)
- Creation to Completion: 7.62 days
- Review Process: 3.75 days

The Unexpected: Much longer documents
## Case Study – Control and Additional Benefits

<table>
<thead>
<tr>
<th>Control</th>
<th>50% time reduction for 1150 documents/month</th>
</tr>
</thead>
</table>
| Additional Benefits | - Better data quality -> less compliance burden  
- Improved communication & collaboration |
Summary

- Performance of the QC Laboratory impacts overall business performance of Pharmaceutical companies

- Major potential improvements
  - Reduction of production time
  - Cost savings
  - Improved product & data quality
  - Reduction of errors
  - Improved compliance
  - Improved communication & collaboration

- Achieving a “Lean Lab”