Pharmaceutical Quality
How We Build and Maintain it Under a Robust Quality System

Juan Andres, Novartis Group Quality
PQRI-FDA workshop, December 1, 2010, Bethesda, Maryland
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Is it okay to be here?

The Issue
We never want to be here!
Why do the same problems keep coming back?

- Complex organization
- Large, diverse businesses
- Cost pressure
- Regulatory evolution
Fixing problems is in our DNA…
But not all solutions stick!
1. Sometimes it feels that we’re running in place

- Recalls
- Complaints
- Recurring deviations
- Human error
2. Consistency isn’t always a good thing…

Cumulative Recalls

Jan  Feb  Mar  Apr  May  Jun  Jul  Aug  Sep  Oct  Nov  Dec

2009  2010
3. Recurring deviations and human error

Deviation in Production Areas

- Recurring (process): 30%
- Recurring (human): 40%
- Non recurring: 30%

Source: internal Site
Note: While this is a high-end example, recurring deviations can reach 85%
4. New business trends bring new issues...

3rd Party vs. Own Production

- **Produced Batches**
  - Own: 85%
  - 3rd Party: 15%

- **Justified Complaints**
  - Own: 60%
  - 3rd Party: 40%

- **Recalls**
  - Own: 40%
  - 3rd Party: 60%
5. We keep having new products…

…on old platforms!
Expectations evolve

Evolution by Decade

1990s
- Data integrity
- Product controls
- GMPs
- ...

2000s
- Sterile Operations
- Information Technology
- ...

2010s
- Pharmacovigilance
- Supply chain integrity
- Clinical Q Oversight
- ...
- ...
We must evolve… systematically!
Of course, we must manage issues

Our Evolution
Beyond managing issues

Approach

Issues Management
React → Police → Enforce

Quality Management
Systemize → Monitor → Adjust
Beyond managing issues

Resource Allocation

Issues Management

Quality Management

Illustrative

Illustrative
Beyond managing issues

Mindset

Issues Management

Quality Management

QUALITY IS COMPLIANCE

QUALITY BEYOND COMPLIANCE
The right system; the right measures
Changing the way we think and act

CONTINUOUSLY

- Metrics & KQIs
  Monitoring & Evaluation

- CAPAs
  Correction & Prevention

PERIODICALLY

- Q Risk Assessment
  Site/Unit

- Product Review
  APR-PQR

- Q-Systems
  Review
Quality Management: a management responsibility

Managing Quality
at all levels of the Organization

Continual Improvement
of Process Performance and Product Quality
Quality Management: a management responsibility

Managing Quality at all levels of the Organization structure

Continual Improvement of Process Performance and Product Quality
- Modern
- ICH-based
- Consistently implemented (across the company)
- Acquisitions: fast adoption
Quality Plans

Continuously

Metrics & KQIs
Monitoring & Evaluation

CAPAs
Correction & Prevention

Periodically

Q Risk Assessment
Site/Unit

Product Review
APR-PQR

Q-Systems
Review

Annual Quality Plan

Internal Audits | Self Inspections | External Audits | Regulatory Intelligence

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Quality Management: a management responsibility

Managing Quality
at all levels of the Organization

Continual Improvement
of Process Performance and Product Quality
Continual Improvement of Process Performance and Product Quality
Continual Improvement

Product Quality Monitoring

- Capability of processes and controls
- Process Stability (variation analysis)
Process Capability and Product Quality Monitoring

The image shows a process capability sixpack of assay for Product A. The figures include:

- **I Chart**: Showing individual values over time with control limits.
- **Capability Histogram**: Displaying the distribution of data within specifications.
- **Moving Range Chart**: Illustrating the range of moving values.
- **Normal Prob Plot**: Demonstrating the normality of the data distribution.
- **Capability Plot**: Detailing within and overall capability indices such as Cp, Cpk, Pp, and Ppk.

Specifications:
- LSL: 10
- USL: 20

Indices:
- Cp: 5.09
- Cpk: 2.48
- Pp: 3.08
- Ppk: 1.5
Quality by Design Manufacturing

- **TRADITIONAL**
- **LEAN**
- **CONTINUOUS**

- **Quality by Design**
- **Continuous Manufacturing**

- **Overall Asset Effectiveness**
  - > 80%

- **Quality**

- **Throughput Time**
  - <10 days
  - 10–40%
  - 40–60%

- **Year**
  - 2005
  - 2010
  - > 2015
3 Continuous Manufacturing

- Flow
- Integration (end to end)
- Integrated control strategy
- Leaps, not incremental
- Incorporate new technology
- Promote mindset change
## Continuous Manufacturing

<table>
<thead>
<tr>
<th>Technology</th>
<th>Upstream</th>
<th>Downstream</th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Existing</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Research stage</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>
## Continuous Manufacturing – examples

<table>
<thead>
<tr>
<th><strong>Upstream</strong></th>
<th><strong>Downstream</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro and Meso reactor</td>
<td>Melt extrusion molding</td>
</tr>
<tr>
<td>Continuous crystallization</td>
<td>Wet extrusion molding</td>
</tr>
<tr>
<td>Reaction classes</td>
<td>Heterogeneous crystallization on crystalline excipients</td>
</tr>
<tr>
<td>Continuous purification</td>
<td>Heterogeneous nucleation on polymers</td>
</tr>
<tr>
<td>Continuous filtration &amp; drying</td>
<td>Co-processing of API and excipients</td>
</tr>
</tbody>
</table>
Continuous Manufacturing – expected benefits
3 Continuous Manufacturing – expected benefits

REDUCE SPACE

- Variability (QbD)
- Asset footprint (40-90%)
- Capital expenditure (25-60%)
- Operational costs (25-60%)
- Inventories
- Development times
Continuous Manufacturing – real examples

**REDUCE**
- Variability (QbD)
- Asset footprint (40-90%)
- Capital expenditure (25-60%)
- Operational costs (25-60%)
- Inventories
- Development times

**BATCH**
### Continuous Manufacturing – real example

<table>
<thead>
<tr>
<th>BATCH</th>
<th>CONTINUOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>-76°C</td>
<td>-10°C</td>
</tr>
<tr>
<td>5 hours</td>
<td>1 minute</td>
</tr>
<tr>
<td>Purity: &lt;70%</td>
<td>Purity: &gt;85%</td>
</tr>
</tbody>
</table>

Source: SK Corporation Korea / BU: Custom Manufacturing Service
Presentation to Novartis: „Use of Continuous Process for the Synthesis of Pharmaceutical Intermediates“
Continuous Manufacturing – economic comparison

<table>
<thead>
<tr>
<th>BATCH</th>
<th>CONTINUOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capacity: 20MT/yr</td>
<td>Capacity: 20MT/yr</td>
</tr>
</tbody>
</table>

Source: SK Corporation Korea / BU: Custom Manufacturing Service
Presentation to Novartis: „Use of Continuous Process for the Synthesis of Pharmaceutical Intermediates“
### Continuous Manufacturing – economic comparison

<table>
<thead>
<tr>
<th></th>
<th>BATCH</th>
<th>CONTINUOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Yield</td>
<td>50%</td>
<td>75%</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>BATCH</th>
<th>CONTINUOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1,000,000</td>
<td>$270,000</td>
</tr>
</tbody>
</table>

-73%

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Continuous Manufacturing – economic comparison

<table>
<thead>
<tr>
<th>BATCH</th>
<th>CONTINUOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$300/kg</td>
<td>$200/kg</td>
</tr>
</tbody>
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Presentation to Novartis: „Use of Continuous Process for the Synthesis of Pharmaceutical Intermediates“
3 Continuous Manufacturing – economic comparison

<table>
<thead>
<tr>
<th>BATCH</th>
<th>CONTINUOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labor Cost</td>
<td>Labor Cost</td>
</tr>
<tr>
<td>$240,000/yr</td>
<td>$120,000/yr</td>
</tr>
</tbody>
</table>

-50%

Source: SK Corporation Korea / BU: Custom Manufacturing Service
Presentation to Novartis: „Use of Continuous Process for the Synthesis of Pharmaceutical Intermediates“
3. Continuous Manufacturing – economic comparison

<table>
<thead>
<tr>
<th>Batch</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>$550/kg</td>
<td>$350/kg</td>
</tr>
<tr>
<td>-36%</td>
<td></td>
</tr>
</tbody>
</table>

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Presentation to Novartis: „Use of Continuous Process for the Synthesis of Pharmaceutical Intermediates“
Quality Management

Managing Quality
at all levels of the Organization

Continual Improvement
of Process Performance and Product Quality
Quality Management and new platforms

**Continuously**

- Metrics & KQIs
  - Monitoring & Evaluation
- CAPAs
  - Correction & Prevention

**Periodically**

- Q Risk Assessment
  - Site/Unit
- Product Review
  - APR-PQR
- Q-Systems
  - Review
- Annual Quality Plan
- Internal Audits
- Self Inspections
- External Audits
- Regulatory Intelligence
Joint Benefit: less reliance on heroic action!
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