Unlocking the Knowledge: The Key to Delivering the Compliance and Business Benefits Outlined in ICH Q10 for Medicinal Product Manufacture

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Unlocking the Knowledge
The key to delivering the compliance and business benefits outlined in ICH Q10

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Agenda

- Introduction to the Research program
- Overview of the Regulatory Drivers
- Review of Recent Regulatory Actions
- Challenges of delivering a holistic approach to the Pharmaceutical Quality System (Q10) expectations
- Review of key relevant findings of recent 'Operational Excellence in the Pharmaceutical Industry' St. Gallen Uni. benchmarking report
- Knowledge is the Key
- How can we utilise familiar OPEX, Lean/ Six Sigma tools to capture this knowledge and deliver the expectations and opportunities for ICH Q10

PSRT Research Program

Aim: The purpose of this research is to develop a science and risk based methodology for use by the Pharmaceutical Industry which will provide a practical integrated knowledge framework for achieving, maintaining and facilitating continual improvement of the 'State of Control' across the entire lifecycle relating to the commercial manufacture of human drug products.

An associated implementation toolset based on lean/six sigma principles will also be developed

Where were you in July 2003?

What were the key regulatory strategies in use in your organisation at that time?

Was your organization introducing new products into your manufacturing facilities?

Preparing for a regulatory inspection?

Perhaps even busy responding to regulatory observations or actions following a recent inspection or audit?
**Quality: A New Paradigm**

In July 2003, at an important ICH meeting in Brussels, a new quality vision was agreed on. This emphasized a risk and science-based approach to pharmaceuticals in an adequately implemented quality system.

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**ICH Q10 PQS – Regulatory Context**

Take note...

- Much of the content of ICH Q10 applicable to manufacturing sites is currently specified by regional GMP requirements.
- ICH Q10 is not intended to create any new expectations beyond current regulatory requirements.
- Consequently, the content of ICH Q10 that is additional to current regional GMP requirements is optional.

However,

- ICH Q10 demonstrates industry and regulatory authorities' support of an effective pharmaceutical quality system to enhance the quality and availability of medicines around the world in the interest of public health.
- Implementation of ICH Q10 throughout the product lifecycle should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

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**Recent Regulatory Action example 1**

FDA Warning Letter to a Danish Firm dated 2nd May 2012

Failure to establish and maintain adequate procedures for validating the device design. Design validation shall include risk analysis, where appropriate, as required by 21 CFR 820.30(g).

For example, your firm's procedure, (b)(4), dated 01/10/2011, does not include or refer to the process to be used when conducting a risk analysis. ... your firm did not establish a process for identifying the potential hazards of the design project as required by the standard being used (b)(4).
Recent Regulatory Action example 2

FDA Warning Letter to a Spanish Firm dated 24th April 2012

3. Your firm has not established scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity [21 C.F.R. § 211.160(b)].

Recent Regulatory Action example 3

FDA Warning Letter to a US OTC Manufacturer dated…..2011

Warning Letter OTC Manufacturer

- Firm's management, including the Quality Control Unit, was not responsive to adverse trend of customer complaints.
- Failure of your Quality Control Unit to ensure a thorough investigation with conclusions and follow up accomplished (two deviations, both 211.192 and 211.198).
- Senior management (includes corporate in this case) is responsible for ensuring the quality, safety, and integrity of your firm’s drug products.

Challenges to Holistic Implementation of QbD Principles

Challenges Identified by McKinsey Report

- Inconsistency of treatment of QbD across FDA – individual by-ind
- Lack of tangible guidance for industry
- Regulators not prepared to handle QbD applications – different waves of understanding
- Unclear regulatory benefits
- Misalignment of internal regulatory bodies – one application does not fit all – need for global harmonization
- Current interactions with companies not conducive to QbD

Additional Implementation Challenges and Gaps at FDA

- Complications of merging new in with the old – changing from empirical to science-based standards
- Heavy workload and limited resources
- Gaps in interactions between review and cGMP
- Need better understanding of the linkage between quality, safety and efficacy
- Need for better utilization of modeling in pharmaceutical development and manufacturing

St.Gallen University OPEX Benchmarking

<table>
<thead>
<tr>
<th>Industry</th>
<th>Pharmaceutical</th>
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<tr>
<td>Number of Production Sites</td>
<td>181 (Total)</td>
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<tr>
<td>- 134 (Formulation &amp; Packaging)</td>
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<tr>
<td>- 38 (API)</td>
<td></td>
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<tr>
<td>- 9 (Biotech)</td>
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<tr>
<td>Number of Companies</td>
<td>91 (Total)</td>
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<td>- Including ten companies of the Top 20*</td>
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Content – Scope

- Enabler Implementation and Performance Metrics (KPIs)

Content – Modules

- Total Productive Maintenance (TPM)
- Total Quality Management (TQM)
- Just-in-Time (JIT)
- Effective Management System

Published 2010, Forward written by ISPE Operations Management CIP

Source: Mastering Plant Complexity and the Impact of Operational Excellence, Prof. Dr. Thomas Friedli, University of St.Gallen, OPEX-Benchmarking
How to achieve Excellence?

Excellence deals with doing the right things (quality, delivery) and doing things right (efficiency, costs)

1. Measure and control the whole picture!
2. Stabilize first, reduce waste second!

Source: Mastering Plant Complexity and the Impact of Operational Excellence, Prof. Dr. Thomas Friedli, University of St.Gallen, OPEX-Benchmarking

What does Top Performance mean for TQM?

Results from 2011 (based on 2010 data)

- A Top Performer has a higher yield and a comparable low cost of quality
- The Top 10% of our sample have a QA/QC-direct-Employees-ratio of 22% compared to this Top Performer’s ratio of 8.5%

<table>
<thead>
<tr>
<th></th>
<th>Average Sample</th>
<th>Top Performer</th>
<th>Lowest 10%</th>
<th>Top Performer</th>
<th>Lowest 10%</th>
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<tr>
<td>Yield</td>
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<td>QA/QC/direct Employees</td>
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<td>22%</td>
<td>8.5%</td>
<td></td>
<td>30%</td>
<td>10%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Source: Mastering Plant Complexity and the Impact of Operational Excellence, Prof. Dr. Thomas Friedli, University of St.Gallen, OPEX-Benchmarking

Acknowledgement

Special thanks to Dr. Thomas Friedli who generously shared his June 2012 presentation

Mastering Plant Complexity and the Impact of Operational Excellence
Prof. Dr. Thomas Friedli
University of St. Gallen, Switzerland

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Unlocking the Knowledge

Unlocking the tacit knowledge within our organisations will be one of the significant factors to successful implementation of effective and efficient Pharmaceutical Quality Systems.

Knowledge Creation- Ikujiro Nonaka

"Knowledge is dynamic, since it is created in social interactions amongst individuals and organisations"

"Without real exchange, you can’t create knowledge. Knowledge creation is a human activity."

"Tacit knowledge is a key component of innovation"


Data to Wisdom - DIKW Model

Path Forward for Implementation

The Challenge

How can we build Knowledge Networks utilising familiar OPEX, Lean/ Six Sigma tools to capture key Tacit Knowledge and manage the delivery of Process Wisdom to enhance Quality Decision Making meeting the expectations and opportunities of ICH Q10?
Currently Developing a Pharma Lean Six Sigma Toolset

Deming’s System of Profound Knowledge

Deming advocated that all managers need to have what he called a System of Profound Knowledge, consisting of four parts:

- **Appreciation of a system**: understanding the overall processes involving suppliers, producers, and customers (or recipients) of goods and services
- **Knowledge of variation**: understanding the range and causes of variation in quality
- **Theory of knowledge**: the concepts explaining knowledge and the limits of what can be known
- **Knowledge of psychology**: understanding the concepts of human nature.

Source: ISPE C&Q Seminar June 2008 Washington: Good Engineering Practice, Nuala Calnan
Deming’s 14 key principles for transforming business effectiveness from Out of the Crisis (1992)

1. Create constancy of purpose toward improvement.
2. Adopt the new philosophy and take on leadership for change.
3. Cease dependence on inspection to achieve quality by building quality into the product in the first place.
4. End the practice of awarding business on the basis of price tag.
5. Improve constantly and thus constantly decrease cost.
6. Institute training on the job.
7. Institute leadership.
8. Drive out fear.
10. Eliminate slogans, as the bulk of the causes of low quality belong to the system and not the work force.
11. a. Eliminate work standards (quotas).
    b. Substitute leadership.
12. a. Remove barriers that rob the worker of his right to pride of workmanship.
    b. Remove barriers that rob people in management and in engineering of their right to pride of workmanship.
13. Institute a vigorous program of education and self-improvement.
14. Put everybody in the company to work to accomplish the transformation. The transformation is everybody’s work.

Source: ISPE C&Q Seminar June 2008 Washington- Good Engineering Practice, Nuala Calnan

Some Useful References