Complacency is not an Option

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Agenda

- Lilly's manufacturing quality transformation journey
- Lilly's quality system
- Control strategy
- Continuous improvement
- Applying lessons learned
- Closing

Lilly Manufacturing Quality Transformation Journey

2001 – 2002

- As a result of a series of inspections, the FDA issued three Form 483s at the Lilly Indianapolis Technology Center, indicating the FDA had concerns about our quality systems and oversight.
- We did not fully listen to or understand the FDA's concerns.
- We were only addressing observations, and were not dealing with our quality problems in a holistic manner.
- FDA ultimately agreed to our voluntary improvement plan.

***Lesson Learned #1**: Look beyond the observations, listen to the signals.*

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Lilly Manufacturing Quality Transformation Journey

2003 - We focused – *we are making medicine*!

We began remediation and taking a holistic quality approach to:

- Organization - leadership changes, added technical resources, training
- Capital investments - facilities, equipment, laboratories
- Technical improvements - manufacturing processes, laboratory assays, sterility assurance
- Integrated quality standards and procedures
- Governance - auditing, oversight, escalation of issues

Remediation efforts were driving us to understand quality as a system.

Lilly's Quality System

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Organization

- Quality unit is an enterprise-wide, global unit
  - Medical, Manufacturing, Marketing Affiliates
  - Head of Quality unit reports directly to CEO, is a company officer, and a member of Lilly's Executive Committee *(14)*
- Manufacturing organization - technical capability, e.g. MS&T, Engineering
- Right people, in the right roles, in both organizations have
  - Leadership: effective partnership
  - Experience and interest in running operations
  - Sense of the business: know operations, holistic decision making
  - Passion for improvement: simplicity and agility
  - Character, capability, curiosity, courage

***Lesson Learned #2**: The organization must staff and partner to design an effective quality system, utilize it, and then improve it.*

ICHQ10 2.4 (a) Management should determine and provide adequate and appropriate resources (human, materials, facilities and equipment) to implement and maintain the pharmaceutical quality system and continually improve its effectiveness.

Governance/Management Oversight

- The governance structure ensures that quality issues are appropriately escalated and resolved, and that quality commitments are met.
  - Includes quality reports to Board of Directors: Public Policy Committee (4x), Science and Technology Committee (1x), full Board (1x), annual quality audit plan reviewed at Board
  - Internal for-cause holistic quality reviews
  - Senior management site reviews
  - Quality management system reviews
  - Product performance reviews
- CEO visits manufacturing plants (*approximately 8 sites/year*)

***Lesson Learned #3**: Appropriate involvement of management is key to ongoing sustainability, not just during times of crisis.*

ICHQ10 2.6 (a) Senior Management should be responsible for the pharmaceutical quality system governance through management review to ensure its continuing suitability and effectiveness.

Governance

Global Manufacturing Quality Lead Team

- **Responsibilities, logistics**
  - Responsible for strategic leadership and oversight of product quality and regulatory compliance for commercial manufacturing operations
  - Meets 3 hours monthly; comprised of most senior manufacturing, quality leaders, plus: MS&T, engineering, continuous improvement, IT, legal, and regulatory members
  - Plans for and prioritizes quality related improvements
  - Ensures appropriate resourcing to achieve quality objectives
- **Site** reviews : reviews of each sites' performance (presented by the site head) related to product quality and quality systems - including organizational changes, metrics, risks, actions, global quality leader recommendations
- **Global** quality system reviews: annual reviews of systems' performance to ensure ongoing effectiveness, and identification of trends

Vigilance in governance even during times of solid performance.

Governance Lessons Learned – Leadership Behaviors

- Don't shoot the messenger
- Listen and internalize – guard against hubris
- People capability and capacity is essential
- Take personal ownership for building business processes
- Don't get distracted

***Lesson Learned #4**: Ask Questions, Listen Carefully, Avoid Complacency.*

ICHQ10 2.5 Internal Communication

(a) Management should ensure appropriate communication processes are established and implemented within the organization.

(b) Communications processes should ensure the flow of appropriate information between all levels of the company.

(c) Communications processes should ensure the appropriate and timely escalation of certain product quality and pharmaceutical quality system issues.

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Integrated Standards & Business Processes

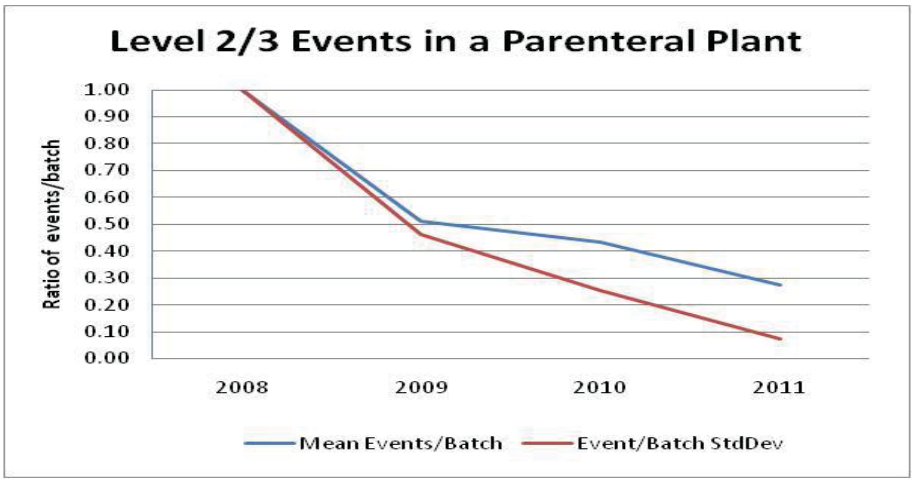
- Integrated Standards (54) organized by themes
  - Quality System; Facilities and equipment; Materials; Production; Laboratory Controls; and Packaging and labeling
- Business Processes are owned by the business with quality input – effective partnerships
  - Operational Excellence standards
  - Common IT platforms
  - Knowing external and internal requirements (references in standards)

***Lesson Learned #5**: The design of standards and business processes must have active involvement of both management and subject matter experts.*

ICHQ10 2.1 (b) Management should:

(1) Participate in the design, implementation, monitoring and maintenance of an effective pharmaceutical quality system;

Tangible Quality Performance



A robust quality system not only improves product quality by reducing events by 70%, but it also provides tangible business results.

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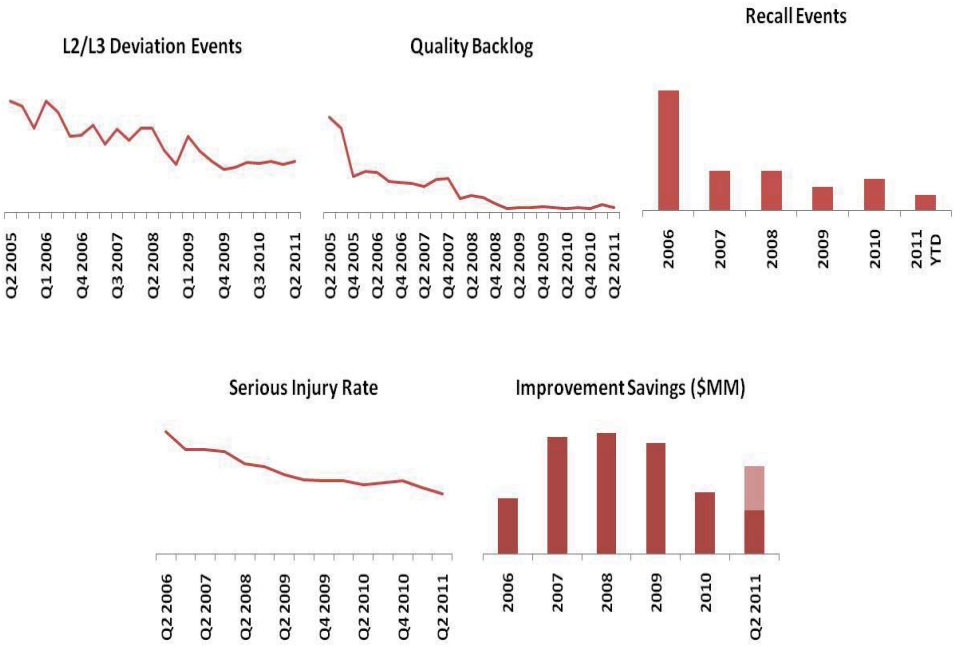
Tangible Business Results



Using quality systems to drive improvements results in good business outcomes.

Operational excellence is the integration of an effective management system, scientific and technical excellence, and a mindset of continuous improvement

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Scientific and Technical Excellence - Control Strategy

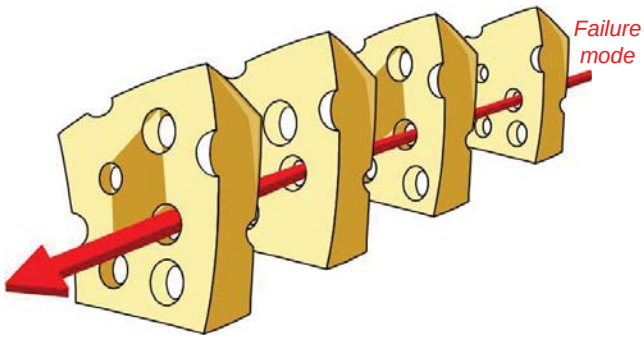
Product Control Strategy	Operational Control Strategy	
Quality by Design →	Operationalize into systems →	Monitor/Improve

• Product Control strategy	• Define operational requirements and controls
	• Define monitoring plan
	• Document control strategy
	• Provide process instructions, tools
	• Establish control charts
	• Assess state of control and capability
	• Respond to signals
	  • Control chart
	  • Deviations
		• Periodic reviews (quarterly, annually)
		  • Process team reviews
		  • Product reviews
		  • Global reviews
		• Assess effectiveness of Control Strategy
		• Improvements
		  • Change management

Development Manufacturing Lead Team	Global Manufacturing Science Lead Team	

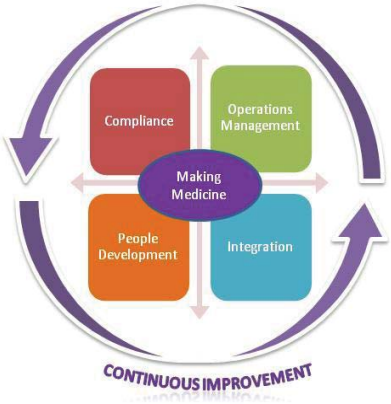
Quality System + Science = Swiss Cheese Model

- Holes are due to design, process, or people failures.
- The pieces of the system are dependent on the other pieces.
- No system is "perfect", thus requiring constant learning and adjustments in pursuit of continuous improvement.



***Lesson Learned #6**: You can design product control strategies and a quality system, but you must be prepared to improve them.*

- Continuous Improvements may be driven by
  - Process & Product reviews
  - Quality System reviews
  - CAPA, Self assessments & Audits
  - Changes in business,
  - Emerging science & technology
  - Changes in regulations, guidance
  - Product portfolio
- Continuous Improvements may include
  - Standards
  - Business processes
  - Organization: People capability & capacity
  - Governance/management controls

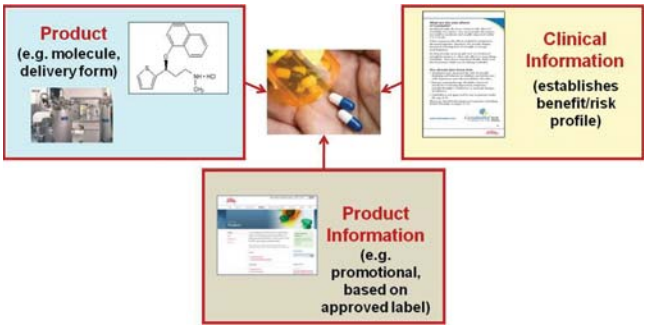


***Lesson Learned #7**: Continuous improvement is a never-ending process.*

ICHQ10 2.1 (b) Management should: (6) Advocate continual improvement

Applying Learning Across the Enterprise Lilly's Integrated Quality System

- We began applying learning from manufacturing to remainder of the company.
- We have been in a state of continuous improvement with our integrated quality system.
  - Safety and Efficacy (Pharmacovigilance, medical research, safety and efficacy information)
  - Customer Information



Enterprise-wide quality system

ICHQ10 Section 2. Management Responsibility
Leadership is essential to establish and maintain a company-wide commitment to quality and for the performance of the pharmaceutical quality system.

Remember…

It's a privilege to come to work every day to discover, develop, make, and market medicine. Every day, we must earn that privilege–not for the regulators, but for our patients, for our customers, and for ourselves.