Medical Quality by Design

“the journey continues”

Jeff Kasher
VP Clinical Development, Eli Lilly & Company
08 – 23 – 2011
Quality as a Culture

The Road to Quality as a Culture.
Vision Statement

The Clinical Development Organization (CDO) will reliably deliver the portfolio with quality, on time, and on budget

- Critical **processes** are clearly defined and efficient, with single-point accountability for key decisions / process steps

- **Sourcing** and capacity decisions are strategic rather than tactical, and leverage opportunities to increase organizational effectiveness

- Run clinical development with a **business mindset**; measure and track performance with effective metrics

- Clinical **strategy, planning, & execution** activities are tightly linked (clear ‘line of sight’). Commitments are made with a full understanding of feasibility
Medical Quality System Redesign
A Single, Integrated Quality System

What we’ve built:

- A streamlined set of global quality system documents (~90% reduction in global documents)
- A comprehensive, process-based approach to support effective implementation - process streamlining, role clarification, and strengthened governance
- Structured to enable FIPNET through requirements applicable internally and externally
- Designed to integrate with other related quality systems (e.g., Lilly Global, Safety, Regulatory, Product Research & Development Quality Systems)

- Clear requirements to meet both compliance and patient expectations
- Management Involvement
  - Escalation
  - Decision Making
- Integrated Standards
- Business Processes
- Organization

• Simple
• Effective
• Efficient
• Agile

• Right People
• Right Role
• Clear Accountability
• Right Span of Control

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CDO Single Process Map

Inputs
- Value Proposition
- Draft Launch Label
- Brand Strategy
- Medical Objectives and Clinical Strategy

Process
- Explore Therapeutic Concept
  - Plan
  - Design
  - Execute
  - Analyze
  - Disclose
- Confirm Therapeutic Benefit
  - Plan
  - Design
  - Execute
  - Analyze
  - Disclose
- Optimize Therapeutic Benefit
  - Plan
  - Design
  - Execute
  - Analyze
  - Disclose

Outputs
- Safety
- Efficacy
- Outcomes
- Product Label • PRA

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Establishing a Quality Foundation

Medical Single Process Map

- Inputs: Value Proposition, Draft Launch Label, Brand Strategy, Medical Objectives and Clinical Strategy
- Process: Explore Therapeutic Concept, Confirm Therapeutic Benefit, Optimize Therapeutic Benefit
- Outputs: Safety, Efficacy, Outcomes, Product Label, PRA

Business Process Management

- Value Proposition: Surveillance
- Brand Strategy
- Medical Objectives and Clinical Strategy

Quality System

- Integrated Standards
- Business Processes
- Management Controls
- Organization

- Clear requirements to meet both compliance and patient expectations
- Simple, Effective, Efficient, Agile
- Right People, Right Role, Clear Accountability, Right Span of Control

Management Involvement
- Escalation
- Decision Making

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Building Quality into Clinical Trials

Clinical Planning
- Approved Clinical Plans
- Medical/Scientific Validity Reviews
- Operational Reviews
- Annual Clinical Plan Reviews
- Chief Medical Officer Oversight

Study Design
- Approved Study Protocols
- Protocol Review Committees
- Change Management

Study Execution
- Investigator Site Selection
- Risk-based Monitoring Program

Data Analysis
- Approved Plans of Analysis
- Analysis Program Validation
- Approval of Analysis Output

Scientific Disclosure & Dissemination
- Disclosure Approvals

Quality Governance
- Deviation Management
- Quality Plans
- Third Party Management Program
- Trial Master File Periodic Reviews
- Quality Audits & Assessments
- Quality Lead Teams
- Metrics Review
Integrated Quality Risk Management

- Deviation Management
- Risk-based Monitoring
- Data Validation & Review
- Sponsor Trial Master File
- Trial Level Safety Reviews

Third Party Management Oversight
# Sourcing Model Distinctions

<table>
<thead>
<tr>
<th></th>
<th>Functional Sourcing</th>
<th>Project Sourcing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Role</td>
<td>Process</td>
</tr>
<tr>
<td>Quality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td>Standards</td>
<td>Lilly</td>
</tr>
<tr>
<td>Quality</td>
<td>Procedures</td>
<td>Lilly</td>
</tr>
<tr>
<td>Work</td>
<td>Payment method</td>
<td>FTE rate</td>
</tr>
<tr>
<td>Work</td>
<td>Forecast Volume</td>
<td>Lilly Function</td>
</tr>
<tr>
<td>Work</td>
<td>Resource Planning</td>
<td>Lilly</td>
</tr>
<tr>
<td>Integration</td>
<td>PM Accountability</td>
<td>Lilly</td>
</tr>
<tr>
<td>Integration</td>
<td>Data Integration</td>
<td>Lilly</td>
</tr>
</tbody>
</table>

* In transition to Future State with redesign efforts
Oversight of Strategic Third Parties

- Executive / Joint Operations Committees
- Quality Councils
- Metrics Reviews
- TPO Review of Standards

- Quality Agreements
- Master Service Agreements
- Operations Guides
- Quality Oversight Plans/Work Plans

- Due Diligence Quality Assessments
- Third Party Audits

- Governance
- Documentation
- Global Medical Quality
- GQAAC

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9/6/2011
Clinical trial monitoring must be driven by: scientific analysis, protocol objectives, and trial data

- **Planning:** Clinical trial monitoring plan which is based on statistical/scientific data elements in the protocol
  - Prioritization of data and processes critical to data integrity and subject protection
  - Development of adaptive study specific monitoring requirements
- **Execution:** Ongoing trial monitoring activities include:
  - Traditional on-site monitoring
  - Statistical data monitoring to assess data trends across sites and trials
  - Internal monitoring of key internal processes
- **Risk-based monitoring benefits:**
  - Enables the proactive identification of areas/sites of risk
  - Establishes the foundation to respond to real-time study data
  - Ultimately ensures that:
    - Clinical data answers the scientific questions/objectives outlined in the protocol
    - Meets regulatory and quality requirements for the safety of study subjects

“Sponsors must be able to answer why they are monitoring what is being monitored”
– Leslie Ball, MD, Director, Office of Scientific Investigations, FDA
Accomplishments

- 107 assessments have been performed year to date.
  - June 2011: 17 assessment performed globally (no critical observations).

- Trends identified in the following areas (further evaluation and response plan needed):
  - Study Documentation (especially site delegation log not available / inaccurate / incomplete)
  - Monitoring / Issue Resolution (especially issues not identified / escalated and / or resolved appropriately)
  - Training / Personnel Qualification
  - Source Document / Data Accuracy

Improvement Opportunities

- January through May 2011:
  - Of the 8 red sites identified from January through May 2011, 2 sites have moved to orange status and 2 have moved to green status. The remaining 4 red sites remain red.
**Strategic Third Party Assessment Metrics**

**Summary – Q2 2011**

<table>
<thead>
<tr>
<th>Critical Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD current version not signed and/or signage incomplete</td>
</tr>
<tr>
<td>Lack of adequate management control to ensure clinical study services are performed by appropriately qualified personnel and conducted in accordance to defined SOP/guidelines/Clinical Management Plan (CMP)</td>
</tr>
<tr>
<td>Issues not identified, escalated and/or resolved appropriately</td>
</tr>
<tr>
<td>Noncompliance to protocol</td>
</tr>
</tbody>
</table>

Only assessment findings owned by the TPO are included in the status. Findings owned by Lilly are not included in the TPO assessment summary.

<table>
<thead>
<tr>
<th>Number of assessments</th>
<th>#1</th>
<th>#2</th>
<th>#3</th>
<th>#4</th>
<th>#5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Critical Issues</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total number Major Issues</td>
<td>53</td>
<td>22</td>
<td>0</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Total number Other issues</td>
<td>134</td>
<td>39</td>
<td>0</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>Total Number of issues</td>
<td>189</td>
<td>62</td>
<td>0</td>
<td>1</td>
<td>56</td>
</tr>
</tbody>
</table>

**Quality Oversight Assessment Top 10 Issues Cited**

- Source documentation missing/inadequate/incomplete to support study data
- Issues not identified, escalated and/or resolved appropriately
- Site delegation log not available/inaccurate/incomplete
- Data entry system/CRF data inaccurate
- Inadequate or insufficient monitoring
- Noncompliance to protocol
- Drug receipt, dispense, return records are missing, inadequate, incorrect
- Monitoring Plan not followed
- Safety Mailings missing/incomplete
- 1572 not available/inaccurate/incomplete
Deviation Metrics
Summary – June 2011

Deviations Created by Level of Criticality -- 12-Month Trend

- Level 1
- Level 2
- Level 3

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Quality Plan Conformance
Summary – July 2011

Quality Plan Conformance (Metric #9)

Projects Open and Overdue (12 July 2011)
No Global Medical Q Plan projects are currently overdue.

Projects Past Due When Completed (12 July 2011)

<table>
<thead>
<tr>
<th>Action</th>
<th>Due Date</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Release Sponsor Trial Master File procedure and related tools.</td>
<td>01 June 2011</td>
<td>10 June 2011</td>
</tr>
</tbody>
</table>

Projects Completed On Time (12 July 2011)

<table>
<thead>
<tr>
<th>Action</th>
<th>Due Date</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Update IMPACT to include missing network investigator site information.</td>
<td>30 April 2011</td>
<td>21 April 2011</td>
</tr>
<tr>
<td>Utilize the LQS Inspection Readiness and MQS Inspection Management processes to ensure readiness for an MHRA or FDA Inspection.</td>
<td>01 July 2011</td>
<td>08 June 2011</td>
</tr>
</tbody>
</table>
Ongoing Focus

• Execution Excellence – Right the first time!
  o Internal adherence to MQS
  o Investigator site performance
  o Third party organization performance

• Medical Quality System
  o Streamlining (e.g., Data Management, Statistics)
  o Continued harmonization of Quality System topics across Medical, Regulatory, and Safety

• Asia Pacific support
• Ongoing inspection readiness

We are continuing to progress on our Quality Journey!
Quality as a Culture

Quality Approach

Quality as a rule + Quality as a system + Quality by design + Quality as a culture

Increasing strategic maturity results in more efficient and effective use of resources

The Road to Quality as a Culture.