Improving QUALITY

presented by:
Ballard H. Graham
Divisional Vice President,
Global Compliance, CRQS
Abbott Laboratories
Introduction – Ballard Graham

FDA – 32 Years

- District Director, Atlanta
- Director of Investigations, Philadelphia District
- Supervisory Investigator, New Jersey
- Resident Investigator, Sioux Falls, SD
- District Office, Detroit

Abbott – DVP, Global Compliance

- International and external audit management
- Liaison with division and site GMP managers
- Recall, field action, 483 response, and warning letter oversight
- Contract manufacturing compliance
- FDA district interface/field relations
- Global corrective action tracking and monitoring
The Cost of Quality

Everyone is concerned about cost...  
...all the time

Quality is only of concern when it becomes an issue.

– anonymous
Impact

Drug manufacturing has generally not been a focus for drug investors. Companies typically provide little disclosure in their annual reports. This report offers a primer on drug manufacturing as an area of increased scrutiny for assessing individual company exposure.

Manufacturing Focus – September 13, 2002

FDA scrutiny has also delayed new drug approvals and caused some drugs to be in short supply. Schering’s Clarinex was delayed by over a year due to manufacturing issues. Lilly’s Forteo and Zyprexa IM have also been delayed due to issues at Building 105 in Indianapolis. Lilly’s Cymbalta appears to be at risk of a delay. Wyeth’s Vypro light has been delayed by over a year due to “dissolution failure” issues. Recent drug shortages largely involve injectables and vaccines.

There are early indicators to tell when a company is potentially getting into trouble with the FDA. This report includes some early warning signs that we believe investors can use to grade each company’s manufacturing risk. We believe early warning signs include drug recalls, seizures, and FDA warning letters. Recalls for contaminated product are especially disconcerting.

Biologics manufacturing has also been a challenge. As science has progressed, drugs have become more complex and difficult to manufacture. CBER Associate Director Robert Yetter says manufacturing issues have delayed six of the 12 active pending BLAs. There is currently a shortage of manufacturing capacity in the drug industry to produce monoclonal antibodies and proteins from mammalian cell cultures. According to recently published analysis, the industry is likely to be capacity constrained through 2006.

Will the FDA’s new manufacturing initiative mark an inflection point for the industry in GMP compliance? In August 2002, the FDA announced a new GMP manufacturing initiative that appears to focus on implementing and formalizing many measures the agency has already undertaken. Guidelines for GMP compliance will be updated and standardized. The last major revisions to cGMP regulations occurred nearly 25 years ago. PhRMA has endorsed the initiative. The greater consistency in FDA reviews and standardization of GMPs are likely to appeal to the industry.
We believe the FDA has increased its scrutiny of drug manufacturing.

In 2001, the FDA stepped up the intensity, but not the frequency, of its manufacturing inspections and enforcement actions. This has resulted in several high-profile cases that have included consent decrees from Abbott and Schering-Plough for deficient manufacturing practices. Lilly has also come under increased scrutiny.

FDA scrutiny has also delayed new drug approvals and caused manufacturing issues. This has delayed six of the 12 active pending BLAs. There is currently a shortage of manufacturing capacity in the drug industry to produce monoclonal antibodies and proteins from mammalian cell cultures. According to recently published analysis, the industry is likely to be capacity constrained through 2006.

Will the FDA’s new manufacturing initiative mark an inflection point for the industry in GMP compliance?

In August 2002, the FDA announced a new GMP manufacturing initiative that appears to focus on implementing and formalizing many measures the agency has already undertaken. Guidelines for GMP compliance will be updated and standardized. The last major revisions to cGMP regulations occurred nearly 25 years ago. PhRMA has endorsed the initiative. The greater consistency in FDA reviews and standardization of GMPs are likely to appeal to the industry.
What did that COST the Industry?
HIGHEST PRIORITY AREAS OF FOCUS

- E-Submissions
- Water Systems
- Part 11
- Management Review
- Plant Consolidation
- Software Quality
- Training
- Document Standardization
- CAPA/Investigations
- Complaint Management
- Validation
- Calibration
Ways to Assure Potential Regulatory Agency Action(s)

- Failing to keep previous commitments
- Limiting the scope of actions responding to the FDA 483 observations
- Lacking direction and priorities regarding Corrective and Preventative Actions
- Shielding top management from the problems
- Having “inexperienced” people interface with regulators
Ways to Assure Potential Regulatory Agency Action(s) - cont.

- Talk is cheap when significant regulatory action is pending, regulators want results
- Underestimating the regulator’s resolve
- Letting down your guard when the fires die down
- Failing to address the intangibles in your facility
  - Poor employee morale
  - Allowing the rumor mill to flourish
The Consent Decree

Every Consent Decree is different and negotiated between the Company and the Government. Once under an FDA Consent Decree, regulatory scrutiny is enhanced, the company comes under the regulatory microscope, problems are magnified, and any problems observed appear to be more significant.

<table>
<thead>
<tr>
<th>FDA CONSENT DECREE</th>
<th>DATE ENJOINED (OFF)</th>
<th>IMPACT ON THE BUSINESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schering-Plough</td>
<td>Entered 2002</td>
<td>$$$$</td>
</tr>
<tr>
<td>Siemens</td>
<td>Entered 1994, off 1994</td>
<td>$$</td>
</tr>
<tr>
<td>Physio-Control</td>
<td>Entered 1992</td>
<td>$$</td>
</tr>
<tr>
<td>American Red Cross</td>
<td>Entered 1993</td>
<td>$$</td>
</tr>
<tr>
<td>CR Bard</td>
<td>Entered 1993</td>
<td>$$</td>
</tr>
<tr>
<td>Barr</td>
<td>Entered 1993</td>
<td>$$</td>
</tr>
<tr>
<td>Parkedale</td>
<td>Entered 2000, was an extension of Warner Lambert’s from 1993</td>
<td>$$</td>
</tr>
<tr>
<td>Puritan-Bennett</td>
<td>Entered 1994</td>
<td>$</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>Entered 1995</td>
<td>$</td>
</tr>
<tr>
<td>Warner Lambert</td>
<td>Entered 1993</td>
<td>?</td>
</tr>
<tr>
<td>merged with Pfizer in 2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Systems</td>
<td>Entered 1996</td>
<td>?</td>
</tr>
<tr>
<td>Centeon, now Aventis-Behring</td>
<td>Entered 1997</td>
<td>?</td>
</tr>
</tbody>
</table>

$ = 1M – 10MM
$$ = 1MM – 99MM
$$$ = 100MM – 499MM
$$$$ = 500MM – 999MM
$$$$$ = Above 1B
Perspectives

- FDA went from a drug-like approach to GMPs to a quality system/process approach for device and diagnostic products.
- FDA plans to extend this approach to drug products.
- This raised the bar on system requirements.
- When a problem is observed in a system, multiple products may be affected.
- The internal environment at Abbott benefited from engaging experienced third-party experts.
The expectations of FDA are clearly ahead of the best third-party certifiers.

The revised Abbott CAPA system was viewed as “best-in-class” by outside experts (including many high-level former FDA’ers). However, it still took 90 days for the Agency to approve the certification.

Updating the production and process controls led back to the design control phase for older products.

Older products are exceedingly difficult to validate to today’s standards or manufacture in today’s CAPA environment. In some instances, validation for such products must be repeated with little or no reliance on previously generated data.
Measure the True Cost of Quality

Not having a common understanding of quality puts more pain into an organization than anything else I have ever known.

Measure the True Cost of Quality: Juran’s Definition

- **Quality costs**: Costs associated with preventing, finding and correcting defective work
- Costs typically run at 20% – 40% of sales

Measure the True Cost of Quality: Juran’s Definition

Prevention costs
Appraisal costs
Failure costs
Internal failure costs
External failure costs

Total Cost of Quality

Six Sigma Perspective

- High-performance, data-driven approach to analyzing root causes of business problems and solving them
- Ties outputs of a business directly to the requirements of the marketplace

Six Sigma Perspective

Goals of Six Sigma

- **Strategic**: Align organization to its marketplace and deliver real improvements (and dollars) to the bottom line

- **Operational**: Move business product or service attributes fully within the zone of customer specifications and shrink process variation, which causes defects that negatively affect customers

# Root Cause Analysis Process

## Six Sigma Problem Solving – MAIC

### Measure

1. **Describe the Problem**
   - What
   - Where
   - When
   - Extent
   - **IS**
   - **IS NOT**

2. **Determine When Problem Started**

3. **Measure Problem Magnitude**
   - Number
   - Code

### Analyze

4. **Identify Potential Causes**
   - Machine
   - Method
   - Man

5. **Analyze Existing Data**
   - Seal Strength
   - Percent Defective

6. **Construct List of Verified Facts**
   - Machine
   - Method
   - Man

7. **Compare Causes to Facts**

8. **Collect Additional Data Until Root Cause Identified**

   - Subgroup
   - Radius
   - Torque

### Improve

9. **Determine Best Solution**

10. **Pilot Solution**

11. **Verify Solution Works**

### Control

12. **Implement Solution**

### Facts

- **FACTS**
  - Machine
  - Method
  - Man
- **FACTS**
  - Machine
  - Method
  - Man

- **FACTS**
  - Machine
  - Method
  - Man

- **FACTS**
  - Machine
  - Method
  - Man

- **FACTS**
  - Machine
  - Method
  - Man

- **FACTS**
  - Machine
  - Method
  - Man

### Control Plan

- **Control Plan**
  - K = 20
  - K = -20
  - Radius
  - Subgroup
  - Percent Defective

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Cost of Quality: Pharmaceutical Industry

What is the cost of quality in the pharmaceutical industry?

- Increased number of personnel and manufacturing resources focused on correcting quality issues

- Loss of product revenue due to:
  - Recalls
  - Delays in drug approvals
  - Product shortages
  - Plant shutdowns

- Unexpected payments (e.g., consent decree)

SalomonSmithBarney, Drug Manufacturing Focus, September 13, 2002
Pharmaceutical Industry

What factors have increased the cost of quality in the U.S.?

1. **Manufacturing issues:** Drugs have become more difficult and complex to manufacture, especially biologics. Manufacturing issues have delayed six of the 12 active pending Biologic License Applications (BLAs) according to Robert Yetter, CBER associate director.

2. **Lack of guidance from FDA:** Last major revision to cGMP regulations was almost 25 years ago. FDA’s approach to manufacturing inspections and regulation has changed significantly over the years, but new written guidance has not been issued. As a result, it is difficult for companies to be clear as to what is considered “current” manufacturing practice.

SalomonSmithBarney, *Drug Manufacturing Focus*, September 13, 2002
Pharmaceutical Industry (cont.)

What factors have increased the cost of quality in the U.S.?

3. FDA inspections: The FDA has increased its scrutiny of drug manufacturing, increasing the intensity, not the frequency of manufacturing inspections and enforcement actions since 2001
   - 1999 – 1,844 inspections
   - 2001 – 1,497 inspections

4. FDA perception: Pharmaceutical industry
   - Lacks efficiency and effectiveness in manufacturing relative to other manufacturing sectors
   - Lacks innovation in the manufacturing sector
   - Is complacent with respect to upgrading systems and validation standards

SalomonSmithBarney, Drug Manufacturing Focus, September 13, 2002
Costs to Pharmaceutical Industry

**Schering-Plough:**
- Consent decree payments possibly exceeding $500 million
- Approval delays of up to one year
- Several product recalls

**Eli Lilly:**
- Warning letters
- New drug approvals slowed
- Several product recalls

**Pharmacia:**
- Nine manufacturing warning letters
- Drug development timeline delays
- Plant shutdown for quality improvements in 1999 and 2001 after receipt of warning letters
- Several product recalls

**Pfizer:**
- One warning letter

**Merck:**
- Warning letters
- Several product recalls
- Vaccine supply shortages

**Wyeth:**
- $30 million payment for deficient cGMP (2000) for operations
- Manufacturing disruptions
- Product shortages
- Production delays

**Abbott:**
- $100 million payment for Consent Decree cGMP (1999)

SalomonSmithBarney, *Drug Manufacturing Focus*, September 13, 2002
FDA Solutions
Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach

- Science-based GMPs (GXPs)
  - Focuses on implementing and formalizing many measures that the agency has already undertaken
  - Updates and standardizes guidelines for GMP compliance

- Collaborative industry – FDA – academic efforts
  - PQRI (Pharmaceutical Quality Research Institute)
FDA Solutions

Process Analytical Technologies (PATs)

Systems for analysis and control of manufacturing processes based on timely measurements, during processing, of critical quality parameters and performance attributes of raw and in-process materials and processes to assure acceptable end product quality.

– Ajaz Hussein
FDA Presentation of PAT (Audio Conference) 4.24.02

- Fosters continuous improvement in pharmaceutical manufacturing
  - High confidence in every unit that gets shipped
  - Nonconforming batches due to process/product issues are minimized
  - Process validation may be minimized due to on-line monitoring
Quality is conformance to requirements. Everything else is bull...

– Harry I. Forsha,

*The Pursuit of Quality Through Personal Change*,
ASQC Quality Press, 1992
Pharmaceutical Industry Solutions

- Implement cultural and structural change within the organization:
  - Changes in approach
  - Creation of new quality organizations within the company with authority and independence to address quality issues
  - Additional staff

- Upgrade validation, computer and other systems in manufacturing areas

- Enterprise systems development

- Collaborate with FDA
Cost of Quality: Other Industries

### Power Industry

- **Quality interruption:** Change (variation) in power that interfered with the normal operation of electrical equipment
- **Cost:** $29 billion annually (U.S. businesses)
- **Costs to industrial customers:**
  - Lost product
  - Equipment downtime
  - Cleanup
  - Restart

Electric Power Research Institute in Palo Alto, CA
Cost of Quality: Other Industries

Power Industry

- **Quality interruption:** In November 2000, power interruptions caused an outage at Amazon.com over the Thanksgiving holiday weekend.

- **Cost:** Loss of $500,000 in revenue, or 20,000 orders for every 20-minute outage.
Cost of Quality: Other Industries
Automobile Industry

- **Quality interruption**: Faulty fuel tank in Ford Pinto
  - In the 1970s, Ford incurred substantial litigation costs because of a faulty fuel tank in the Ford Pinto. Ford had conducted a cost-benefit analysis to determine if the Pinto should be recalled to repair the fuel tank and decided to save money by leaving the faulty fuel tank in place.

- **Cost to customers**: Loss of life, substantial injuries, loss of property

- **Cost to Ford**: Over $6.5 million in litigation costs, loss of customer loyalty and trust

Cost of Quality: Other Industries
Automobile Industry

- **Quality interruption**: Defective PROM controlling the fuel injector in General Motor’s pickup truck failed
  - In 1992, the Alabama Supreme Court awarded a grandfather $7.5 million in punitive damages after his grandson was killed in an accident because of the defective PROM

- **Court ruling**: $7.5 million in punitive damages awarded to Johnston was justified because GM “saved approximately $42 million by not having a recall or otherwise notifying purchasers of the problems related to the PROM”

*Southern Reporter, 2nd Series, volume 592, pages 1,054 and 1,061.*
The Cost of Quality

ike information technology –

Quality has become a strategic necessity

– Alfred West, Jr.
Improving QUALITY

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Ballard H. Graham
Divisional Vice President, Global Compliance, CRQS
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