Quality Management in a Virtual Environment

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EVP Quality and Compliance, Coherus Biosciences

West Coast PDA
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Biosimilars - the second wave of biotech
-an evolving regulatory and manufacturing landscape

• ~ 61 Biosimilars in Review at FDA

• First US Approvals…
  • Sandoz – Neupogen biosimilar
  • Amgen – Humira biosimilar
  • Sandoz – Enbrel biosimilar
The Eruption behind the Tsunami…

Surge in Patent Expirations

Healthcare Reform/Regulatory Enablement

Analytic Tools Enable Comparability

"Humira’s growth was a little more than we expected and price increases in the United States are probably a big reason," said Morningstar analyst Damien Conover. Humira

Forbes

Drug Prices Defy Gravity -- Until The Patent Expires

“[biosimilars] will potentially provide our patients with very effective therapy at a lower cost.”

-Jonathan Kay, MD
A lack of competition often results in high prices

THE WALL STREET JOURNAL.

550% over eight years
Coherus BioSciences

- Founded 2010
- Solely focused on developing Biosimilars
- Public Pipeline
  - Neulasta biosimilar – filed BLA
  - Enbrel biosimilar – Ph 3
  - Humira biosimilar – Ph3
  - Avastin biosimilar
  - Lucentis biosimilar
- Coherus outsources its manufacturing
  - Provides access to modern, $multi-million plants
    - GMP facility
    - GMP equipment
    - Skilled operators
    - Quality systems
Outsourced manufacturing to top-tier US and EU contract manufacturers
Capacity - CMOs are expanding and provide alternatives to hugely expensive plants

- “Fujifilm Diosynth Biotechnologies expands cell culture manufacturing capacity with addition of two new 2,000L single-use bioreactors”
- “CMC Biologics, Inc., announced today a plan to expand its global manufacturing capacity by more than 30,000 liters”
- “Rentschler Biotechnologie expands European manufacturing capabilities with GE Healthcare Life Sciences bioprocess Technologies”
- “DSM celebrates opening of new cGMP facility for biopharmaceutical manufacturing”
- And Samsung…
Quality - CMOs with new, modern facilities help avoid compliance issues associated with aging facilities

- WHO
  - *Identified Production as the most problematic area in plant inspections.*

- FDA Warning Letters
  - “This design is not conducive for controlling the system’s microbial and endotoxin levels.”
  - “The foregoing examples are of serious CGMP violations…”

Owner and the contract facility are both responsible for CGMP

“FDA could also hold the Owner liable responsible for CGMP failures, or for oversight failures”
Careful CMO selection can help avoid compliance issues
Some regions have a high incidence of warning letters

Warning Letters 2015
Office of Manufacturing Quality

<table>
<thead>
<tr>
<th>Company/Individual</th>
<th>Product/Issue</th>
<th>Issue Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhejiang Hisun Pharmaceutical Co., Ltd.</td>
<td>CGMP/Active Pharmaceutical Ingredients (APIs)</td>
<td>12/31/2015</td>
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<tr>
<td>Cadila Healthcare Limited</td>
<td>CGMP/Active Pharmaceutical Ingredients (APIs)</td>
<td>12/23/2015</td>
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<td>Sun Pharmaceuticals Industries Ltd.</td>
<td>CGMP/Finished Pharmaceuticals</td>
<td>12/17/2015</td>
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<td>Chan Yat Hing Medicine Factory</td>
<td>CGMP/Finished Pharmaceuticals/adulterated</td>
<td>12/15/2015</td>
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<td>Dr. Reddy’s Laboratories Limited</td>
<td>CGMP/Active Pharmaceutical Ingredients (APIs)</td>
<td>11/5/2015</td>
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<tr>
<td>Sandoz Private Limited</td>
<td>CGMP/Finished Pharmaceuticals/adulterated</td>
<td>10/22/2015</td>
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<td>Unimark Remedies Ltd.</td>
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<td>Jaychem Industries, Inc.</td>
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<td>Pan Drugs Limited</td>
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<td>Mylan Laboratories Limited</td>
<td>CGMP/Finished Pharmaceuticals/adulterated</td>
<td>8/6/2015</td>
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<td>Sgra Labs Limited</td>
<td>regulations for testing finished pharmaceuticals and active pharmaceutical ingredients (APIs)</td>
<td>7/23/2015</td>
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<td>Valuedira Specials</td>
<td>CGMP/Finished Pharmaceuticals/adulterated</td>
<td>8/21/2015</td>
</tr>
</tbody>
</table>

- India – 12
- China – 3
- EU – 2
- Other – 3
- USA – 0
- Germany, France, Denmark, The Netherlands, UK, Spain - 0
Essential elements for quality outsourced manufacturing

• Modern facility design & construction
  • Best in class equipment
• Efficient manufacturing operations
  • Streamlined technology transfer
• Compliant Quality Systems
  • Highest quality biosimilars
Personal Observations - “When CMO’s Fail”

• Underestimate capability to handle complexity and transfer work from Process sciences to Op’s

• Support functions inadequate
  • Staffing levels in Quality and Warehousing
  • Experience level across Op’s, Quality, and Validation

• Infrastructure is not resourced or maintained
  • Ageing and/or re-purposed facilities
  • Obsolete and/or customized Manufacturing Execution Systems (MES)
  • Deferred maintenance to squeeze more capacity
Leading Indicators and Red Flag Events

• Quality:
  • QA ‘on the floor’
  • Deviation notification time and closure time
  • Backlogs for batch release, cleaning validation, change overs

• Operations:
  • Experience level of floor supervisors
  • Off shift coverage
  • Use of contractors, percentage of shift
  • Turnover
Selecting high quality CMOs

Screening - Request for Information

<table>
<thead>
<tr>
<th>Company Information</th>
<th>Answer</th>
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<tbody>
<tr>
<td>Company name</td>
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<tr>
<td>Company address</td>
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<tr>
<td>Company web page</td>
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</tr>
<tr>
<td>Company location(s)</td>
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<tr>
<td>Board of Directors</td>
<td></td>
</tr>
<tr>
<td>Executive Leadership</td>
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<tr>
<td>Company Age</td>
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<table>
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<tr>
<th>Financial Information</th>
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<tbody>
<tr>
<td>Private or Public</td>
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<tr>
<td>Source of funding / Future plans</td>
<td></td>
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<tr>
<td>Last year turnover</td>
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<tr>
<td>Last year gross margin</td>
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<tr>
<td>Last year profit</td>
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<tr>
<td>Last Company Annual Report</td>
<td></td>
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<tr>
<td>List of partners</td>
<td></td>
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<table>
<thead>
<tr>
<th>Employees</th>
<th></th>
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<tbody>
<tr>
<td>Production</td>
<td></td>
</tr>
<tr>
<td>R&amp;D</td>
<td></td>
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<tr>
<td>Marketing and sales</td>
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<tr>
<td>Regulatory</td>
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<tr>
<td>Analytical and QC</td>
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<tr>
<td>Quality</td>
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</tbody>
</table>

- Financial stability
- Employees tenure and experience
- Location
- Regulatory history
- Analytical capability
- Mfg scale, commercial history
- PD capability
- Quality systems
- Client references
# CMO Scorecard

<table>
<thead>
<tr>
<th>Selection Criteria</th>
<th>Description</th>
<th>Importance</th>
<th>Rating</th>
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<tbody>
<tr>
<td><strong>Facility</strong></td>
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<td></td>
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<tr>
<td>Location</td>
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</tr>
<tr>
<td>Age/Year built</td>
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<td></td>
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<tr>
<td>Date of last renovation</td>
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<tr>
<td>Total area / Classified area (ft²)</td>
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<tr>
<td>Area classifications</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Quality of architectural finishes</td>
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<td></td>
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<tr>
<td>Appropriate segregation</td>
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<td></td>
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<tr>
<td>Success rate</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Equipment Capability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equipment age</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>State-of-the-Art</td>
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<td></td>
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<tr>
<td>Calibraton and PM program</td>
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<tr>
<td>Qualified</td>
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<tr>
<td>Additional equipment required for process</td>
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</tbody>
</table>
Contract manufacturing oversight

- FDA Guidance
- “both Owners and Contracted Facilities must work together to establish and maintain quality oversight of contracted manufacturing operations.”
  - Quality Agreement (§ 211.22(d))
    - notifications, raw materials, audits, compliance, change control, deviations, responsibilities, laboratory controls, documentation
  - Risk Assessment
  - Facility audits
  - CMO Quality Systems
  - Person-in-Plant
  - Batch Record review
  - Certificate of Compliance
Technology transfer is essential to quality CMO manufacturing and ensuring process performance understanding.
Technology transfer risks and mitigation

- Communication
- Unclear deliverables
- Incorrect batch record
- CPPs unclear to operators
- Buffer preparation
- Inadequate chilling capacity
- Column packing criteria

- F2F project meetings
- Technology transfer protocol
- Process descriptions/Process model
- Process database & control strategy
- Tech transfer pilot run
- Facility fit
- Risk assessment
Effectiveness of inputs and controls in understanding CMO Performance

- More Effective
  - Quality Agreements
  - Joint operational reviews focused on Metrics/Problems

- Less Effective
  - Quality Systems Audits
  - Person in the Plant

Regulatory Inspection history
A well-trained rained Person-in-Plant proactively prevents process problems

- Closely observing operation
  - operator experience/knowledge
  - operator system check
- Historical process data
- Clipboard for taking notes
- Calculator
- Trained Engineer
**Contracted Facility Meeting Management**

“Owners should monitor and review the performance of the Contracted Facility and identify and implement any needed improvements” – FDA Guidance

<table>
<thead>
<tr>
<th>Review items</th>
<th>CMO Steering Ctte</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose</strong></td>
<td>Provide strategic oversight, approval and prioritization</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Quarterly</td>
</tr>
<tr>
<td><strong>Attendees</strong></td>
<td>Senior executives and key managers</td>
</tr>
<tr>
<td></td>
<td>Responsible Executives: CTO, Head of Quality, Business Dev</td>
</tr>
<tr>
<td><strong>Output</strong></td>
<td>Quality review, schedule commitment, capacity plan, resource and budget allocation, agreement terms, issue resolution</td>
</tr>
<tr>
<td><strong>Agenda</strong></td>
<td>Quality performance - Deviations – major/critical Lot release, Success rates, Yields, Release times Upcoming initiatives - process improvements, facility changes Team communication</td>
</tr>
</tbody>
</table>
Quality Agreements- a few key requirements for customers

- Reporting requirements for deviations
- Customer final approval of deviation investigation plans and investigation closure/CAPA
- Customer final approval of validation plans and acceptance criteria deviations and failures
- Resolution process for design of process validation studies
- Participate and roles/responsibilities in PAI
Virtual Companies need a Virtual SME Team

- Establish a team of external consultants with particular expertise:
  - Microbiologist
  - Virologist
  - Drug product visual inspection expert
  - Drug substance technical GMP expert
  - Drug product technical GMP expert
  - Qualified Person system expert
Scenario for a CMO strategic alliance

• Overall summary
  • Impressive process and analytical development capabilities – modern, spacious, well staffed.

• Value Proposition
  • Combined PD & Mfg service. Reduced fees and scheduling flexibility

• Facility
  • Modern single-use clinical manufacturing, 24X7 operation. Spacious labs, dedicated analytical

• Quality/Regulatory Systems
  • Established systems. Good Inspection and Audit history. Recalls/BPDR’s

• Financial Stability
  • High market capitalization and reserves, stable ownership

• Cultural Fit
  • Good synergy with mission and culture: Fast, smart, flexible
Shared outsourcing construct for enhanced quality and flexibility

- Modern, modular manufacturing facility (e.g., 6 x 2000 L bioreactors)
- CAPEX $70MM
- Client reserves 50-100% facility capacity
- CMO gains income certainty
- Client gains additional control over quality system
Summary: Carefully maintaining a Quality culture for outsourcing can result in very consistent product quality

- Careful CMO selection
- Superb technology transfer
- Modern facilities and equipment
- Written agreements
- Person-in-Plant
- Monitor and communication
- “Owner” owns it

Somewhat greater product quality consistency than the originator
Acknowledgments

- Peter Walter, Coherus Biosciences, for his extensive contributions to this presentation