Track 4: Manufacturing, Risk Management, and Quality Assurance
How to Prevent, Detect, and Respond to Data Integrity Events

Moderators:
Paula Katz, FDA and Joseph Famulare, Genentech
About Data Integrity…

Familiar definitions…

Requirements for complete, consistent, and accurate data

Underpinning of CGMPs (minimum requirements, basis for “adulteration”)

Evolving concepts…

Electronic (just like paper—even with white-out), metadata, audit trail, system validation

Essential to our 21st-century quality vision…

Patient safety and consistent access to effective drugs

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector…”
The Data Lifecycle: Beyond ALCOA

Good documentation practices (familiar conception; Part 11)

<table>
<thead>
<tr>
<th>ALCOA</th>
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<tbody>
<tr>
<td>Attributable</td>
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<tr>
<td>Legible</td>
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<tr>
<td>Contemporaneous</td>
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<tr>
<td>Original or true copy</td>
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<td>Accurate</td>
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Why would documentation practices need modernization?

Think: Risk management across entire data lifecycle
Data movement (physical) through supply chains
Quality culture/scientific culture: source information
Do you have a data integrity compliance plan?
Data Integrity and the Big Picture

- Essential component of our sharper focus on quality
- Systematic approach to preventing systemic data flaws
- Increase knowledge as we re-visit data in lifecycle approach

- Understand costliness of data integrity failures: reputation, money, long-term remediation;
- regulators are likely to work better with firms that lead in carrying the responsibilities for their data integrity plans and plan execution

- Understand that data integrity modernization is part of the challenge and gratification represented in quality management systems

- We are on the precipice of something fun! (e.g., Q12)
Continuous Manufacturing

Moderators: Thomas O’Connor, FDA and Diane Zezza, Novartis
Speakers and Panelists: Yanxi Cain, Novartis; Douglas Mans, GSK; Hayden Thomas, Vertex; Rapti Madurawe, FDA
Continuous Manufacturing: An Emerging Technology

• Opportunities for All Stakeholders: Patients, Regulators, and Industry
• Truly achieve product quality by design
• Perceived Benefits
  • Data rich environments leads to deeper process understanding
  • Reduced variability through the adoption of precise control
  • Reduction in equipment footprint requirements
  • No scale-up, more reliable manufacturing, and more agile and responsive supply chains
  • Increased process efficiency and reduction in processing time per unit dose (minutes vs. days)
  • Rapid response to drug shortages, emergencies, patient demand
Common Themes: Batch Definition

- Batch and lot definition in the CFR does not hinder the implementation of CM
  - 21 CFR 210.3 defines a batch as “a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits and is produced according to a single manufacturing order during the same cycle of manufacture”.
  - Additionally, a lot is defined as “a batch, or a specific identified portion of a batch, that has uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.
- Each company represented applied the definition of batch, amount of time, amount of product produced, or event, based on the specific process and business drivers but still able to comply with the regulations
Common Themes: Material Traceability

- Importance of understanding material flow
  - System dynamics including residence time distributions (RTD)
  - Key area of process understanding for process design and development of control strategy
  - Ability to trace and segregate conforming vs non-conforming product
  - Understanding may include development of process models
  - Aspects can be communicated to regulatory bodies to facilitate review
Common Themes: Control Strategy

- Control strategy may need to incorporate more advanced approaches
  - Establishing criteria for state of control (e.g. Start up and shutdown)
  - PAT for in-line monitoring
  - Real time release testing
  - Model based controls
  - May increase complexity
  - Large volume of data for analysis

- Product quality risk management — needs to be documented and communicated
- Quality decisions are made in real time
Takeaways

• Regulatory expectations are the same for CM as for traditional batch manufacturing regarding the science and risk-based understanding and control of processes
• Dialog and alignment between industry and regulators important for implementation
• Additional opportunities to request early communication with FDA: Emerging Technology Team: CDER-ETT@fda.hhs.gov, CMC meetings, pre-operational visits
• Regulatory and quality is developing – still work to done
  • Continuous Process Verification versus Validation
  • Integrated product specifications for integrated end-to-end process (raw materials to drug product)
  • Dossier content
  • Application of existing specific guidance needs to evaluated (e.g. SUPAC)
  • Start of shelf life
How to Monitor, Control, and Improve Product Quality using Process Capability

Moderators:
Barbara Allen, Eli Lilly & Company and Larisa Wu, FDA
Session outline

Speakers & Panel Participants:
• Pharmaceutical Product Quality, Quality by Design, cGMP, and Quality Metrics – Lawrence Yu, FDA
• Using Control Charts to Evaluate Process Variability – Daniel Peng, FDA
• Quality as a Foundation for OPEX – Thomas Friedli, University of St. Gallen
• The Journey from Good to Great: Process Monitoring Leads to Improving Product Quality – Martin VanTrieste, Amgen
• Process Capability and Relationship to Supply Chain – Bryan Winship, Mylan
• Process Capability and Relationship to Quality Management – Barbara Allen, Eli Lilly
Key discussions

- **Process capability** is a leading, useful indicator of quality; however, its calculation is relatively complex.
- **Quality system** should achieve product realization, establish and maintain a state of control, and facilitate continual improvement.
- Quality is the foundation of **operational excellence**.
- **Statistical process control chart** is a valuable tool.
- Concept of capability extends across the **supply chain**.
- **Quality culture**: shift from compliance and meeting specifications to understanding and controlling variability in processes and product.
- **Quality metrics** are used by firms to manage internal operations. Link between FDA metric program & process capability generated engaged conversation.
Session outline (cont.)

Questions discussed

1) Other approaches to process capability seen or suggested, and any experience to share?
   - Emerging topic of conversation. Work by one professional group to be published shortly.

2) Key enablers and challenges:

   Challenges:
   - Specifications.
     - Need mechanism to address post approval changes - globally,
   - Small number of lots.
   - Newer products, esp. accelerated development

   Enablers:
   Leadership focus, Human error prevention programs
Action items

- Continued dialogue is recommended including specification setting and update
- Share experience of the industry beyond the conference forum

Take-home messages

- Manufacturing processes and product quality variability should be understood and controlled
- Quality is the foundation for superior operational excellence (OPEX) performance
Thanks for sharing!
How to Identify Critical Quality Attributes and Critical Process Parameters

Moderators:
Scott Furness, FDA and Bruce Johnson, Perrigo
What’s really so “critical”?  
Introduction by Jennifer Maguire and Daniel Peng of FDA

From Quality Target Product Profile (QTPP) to CQAs  
(Begin with the end in mind)

• QTPP summarizes (prospectively) elements of quality, safety, and efficacy
• QTPP forms the basis for development of the CQAs and largely determines which Q attributes are “critical”

From Critical Quality Attributes (CQAs)

• CQAs are used to make design and optimization decisions and to identify critical material attributes (CMAs), critical process parameters (CPPs), and control strategy through a continuum of risk assessment & structured experimentation

CMAs → Pharmaceutical unit operation → CPPs → CQAs
Quality by Design (QbD)
illustrative submission examples from FDA

1. A sponsor who says, “None of the quality attributes are “critical”
   because fixed all MAs and PPs for all key processing steps
   → Agency’s comment: **All MAs and PPs are potentially critical** due to limited
   characterization of the sources of variability and inadequate understanding of the impact
   of CMAs and CPPs on the drug product CQAs

2. A sponsor implemented significant control of the CQAs with in-process
   or at-line measurements via NIR spectroscopy
   → Agency’s comment: The focus of the review “Controls of Critical Steps and
   Intermediates” → NIR test method

Examples/perspective from Generic Pharma

(Bruce Johnson, Perrigo)

- Delineated different paradigm, timelines & drivers from NDA product development
- QbD implementation is **scientific and** strategic that should be fully integrated in
  product development
- Leveraging documented prior knowledge is key
  Continuous improvement; via ICH, FDA (ex. MaPP 5015.10), CRLs, USP
A closer look at CPP-CQA relationships

• Developed an approach that utilizes statistical tools for consistency, while still incorporating scientific judgment and a holistic view of the control strategy

• Perhaps the CPP-CQA relationship is statistically significant, but is it practically significant?

New tools from statistics that add to assessment of design space

Presentation by
Ke Wang, Pfizer

Identification of CPPs based on CQAs and Mechanistic Process & Product Understanding: Brivanib as a case study (wet granulation)

• Stress on striving for deeper mechanistic understanding of the process & formula

• Focusing on one PP unit operation to assess control space may be misleading

Presentation by
Ajit Narang, BMS

Tools: FMEA, Fishbone, Databases; DoE; new analytics, in-process, at-line, off-line
Select questions & discussions items

1. Overall, continued conversations to foster greater transparency
2. Is it required to use “critical,” to denote CPPs? Not necessarily, just clarify and be consistent whatever you wish to call it in pharm development section
3. How many “high-risk” CQAs are the right number?
4. Focus on the vital few: but how many are vital?
5. When is range of “criticality” sufficient?

→ Further clarity from FDA vs sponsor-ownership control strategies

6. Can documented prior knowledge be used to eliminate structured experimental studies to determine control space & strategies “(i.e. theory of first principles)?

7. Broadly, are CQAs focused on process control or truly relevant to product safety & efficacy?

8.