Continuous Manufacturing -
Alignment with Quality Risk Management (QRM) Principles

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Senior Regulatory Consultant
Agenda

1. Leverage QRM – Take home messages
2. Regulatory/ Industry QRM Overview
3. Closed Systems for Continuous Bioprocessing
4. mAb Production using Advanced Continuous Processing Technologies
5. Viral Clearance Filtration – QbD overview & continuous process validation approach
6. Concluding Thoughts – Regulatory Expectations
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Leverage QRM – Take Home messages
Prior to ICH Q13
How to leverage a quality risk management approach

1. Principles of Practice

Even though continuous bioprocessing is a different manufacturing approach, the same foundation principles can be utilized to manufacture a biologic drug product that is safe and effective.

2. Process & Product Understanding

The first recombinant monoclonal antibody (mAb) was approved as a human therapeutic 35 years ago. A templated process has been in place for decades. General industry knowledge is more than sufficient to shift to continuous manufacturing.

3. Key Factors to Consider

What are the areas of concern when moving from batch to continuous bioprocessing? It is important to focus and leverage understanding of adventitious agent risk mitigation and overall control strategy.

4. Leverage Advanced Design

Technologies have advanced both in manufacturing equipment and testing approaches. Let’s discuss how single-use, closed systems, and others could mitigate the risk of product quality issues.
Regulatory / Industry QRM overview
Timeline – Regulatory Efforts to Shift Mindset in Pharma/Biopharma Industry to Quality Risk Management (QRM) Approach

US FDA Warning Letters (2006-2013) - The majority of citations indicate that there are problems with faulty (20%) or absent (80%) risk assessment.

2015/2016 - PDA Quality Risk Management Benchmarking Survey – “the full benefits of QRM have not yet been fully realized”

Review of QbD dossier submissions in EU* - The implementation of QbD for biologics has been quite rare (7% of all QbD dossiers) and virtually all from large multinational companies.

Legend:
- FDA – US Food and Drug Administration
- ICH – International Conference on Harmonization
- QbD – Quality by Design (not testing!)
- PDA – Parenteral Drug Association

Regulators encourage innovation – Why is the industry not moving?

“Let me just step back another step and say — and this would also disturb some people — that I really think the culture of regulation that we had over the years, [produced] a kind of a fear relationship. And I am still told that industry is in a state of fear, many of them, of FDA. That kind of a fear relationship is not going to grow a quality culture, because there is a fear of adverse consequences... That is antithetical to the idea of a quality culture, where people own quality and say, ‘we can stand up to the FDA because we make a quality product, and we know it and we monitor it, and we are proud of it. That is our quality culture.’”

Transcript from April 2015 International Society of Pharmaceutical Engineering (ISPE), quality metrics meeting. Quoted by Dr. Janet Woodcock, currently acting commissioner of the US FDA and head of CDER.
Regulators Encouragement for...
A paradigm shift in manufacturing operations regulatory oversight

<table>
<thead>
<tr>
<th>Rule-Based</th>
<th>Risk-Based Compliance</th>
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<tbody>
<tr>
<td>“Box checking” approach—or dotting i’s and crossing t’s—in order to ensure your organization is obeying prescribed rules and regulations.</td>
<td>Depends more heavily on analysis in order to circumvent risks or determine risks worth taking</td>
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<tr>
<td>Quality by “testing”</td>
<td>Quality by “design”, based on ICH Q8</td>
</tr>
<tr>
<td>Subscribing to established rules</td>
<td>Spurring new and innovative processes</td>
</tr>
<tr>
<td>Tactical</td>
<td>Strategic</td>
</tr>
<tr>
<td>Risk Aversion</td>
<td>Value Creation</td>
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<tr>
<td>Driven by a <em>siloed</em> compliance department or <em>siloed</em> initiatives in various departments.</td>
<td><strong>Integrating</strong> departments, technology systems and processes is necessary to determine the <em>overarching</em> risks and how they should be handled—whether it’s to avoid their implications or drive value</td>
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</table>
“A number of technologies and resources are available that can facilitate conformance with CGMP and streamline product development, including use of:

- **Disposable equipment** and process aids to reduce cleaning burden and chances of contamination

- **Commercial, prepackaged materials** (e.g., WFI, pre-sterilized containers and closures) to eliminate the need for additional equipment or for demonstrating CGMP control of existing equipment

- **Closed process equipment** to alleviate the need for stricter room classification for air quality

- **Contract or shared** CGMP manufacturing facilities and testing laboratories (including specialized services). For example, some academic institutions have developed shared manufacturing and testing facilities that can be used by institutional sponsors.”
Monitor and Control Quality via Partnership with Supplier

“Only a partnership with a SUS* supplier can ensure that quality is as good as, or better than what is achieved with traditional systems.”


*SUS = Single-Use System

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**End User**
- Process and Manufacturing Knowledge
- System Design and Operation
- Product and Patient Knowledge
- Internal Procedures and Controls
- Risk Tolerance / Past Experience

**Supplier**
- Experience across a variety of processes
- Material/Component Knowledge
- Product/Service Technical Expertise, including qualification and design
- Product Manufacturing and Controls
- Product Shipping and Handling Best Practices
Closed Systems = bioburden control
Why Closed Systems?

Closed-system processing using single-use technology might be an attractive option for a range of biomanufacturers with different motives. These could include:

- Continuous manufacturers operating processes for many weeks at a time and wanting to avoid a build-up of bioburden within their equipment
- Reduce Facility Costs
- Scenarios where temporary bioproduction is required.

Advantages:

- The risk of contamination is greatly reduced, due to the physical barriers protecting the product from human contact.
- Closed systems reduce operating time by relying less on operator handling and more on pre-assembled components.
- Operations can be performed in lower classification cleanrooms reducing the costs
Closed system life cycle – emphasis on bioburden control

**Pre-use:** System is prepared to the required level of integrity, cleanliness, and bioburden.

**In use:** The closed system is in production, known as “closed processing.” Connections and disconnections are critical in the design to maintain closure; mitigate risk with sterilizing grade filters.

**Post-use:** Measurements should verify that closure was maintained during processing. If the system or its components are cleaned and sanitized, storage and/or transport should protect their closure.
Closed bioprocess
Regulators highlight contamination control strategy*

Contamination Control

Adventitious Agents
- Viruses
- Bacteria
- Fungi

Product Variability
Product Degradation
Product Modification
Changes in impurity profiles
Increase in levels of endotoxins

* (1) Perform risk assessments on a periodic basis and (2) Continuous improvement in quality risk management

Source: Case Studies of Microbial Contamination in Biologic Product Manufacturing | American Pharmaceutical Review - The Review of American Pharmaceutical Business & Technology
Risk Factor Hierarchy for Microbial Contamination

Source: Case Studies of Microbial Contamination in Biologic Product Manufacturing | American Pharmaceutical Review - The Review of American Pharmaceutical Business & Technology
## Bioburden control
### What regulatory findings have happened historically?

<table>
<thead>
<tr>
<th>Issue</th>
<th>Corrective Action</th>
<th>Issue</th>
<th>Corrective Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems with the sampling devices</td>
<td>Replacement of a membrane valve in the sampling device</td>
<td>Cleaning, storage and reuse of UF/ DF systems</td>
<td></td>
</tr>
<tr>
<td>Addition valve issues</td>
<td>A preventive maintenance plan for valves was instituted.</td>
<td>Assessment of the water for injection (WFI) system and transfer lines</td>
<td></td>
</tr>
<tr>
<td>Incorrectly fitted components</td>
<td>Installation SOPs were updated with pictures/figures.</td>
<td>Revisions to bioburden limits based on process capability</td>
<td></td>
</tr>
<tr>
<td>Missing O-rings</td>
<td>Replacement of O-rings</td>
<td>Sanitization of buffer tanks</td>
<td></td>
</tr>
<tr>
<td>Incorrect installation and deformation of</td>
<td>All installation SOPs were updated and employees were trained on the</td>
<td>Validation of hold times and storage conditions of process intermediates</td>
<td></td>
</tr>
<tr>
<td>an air filter after sterilization</td>
<td>revised versions.</td>
<td>Introduction of in-process bioburden reducing filters (in cases where there were no filters before the UF/DF steps)</td>
<td></td>
</tr>
<tr>
<td>Inadequate slope of a condensate line</td>
<td>SOPs were updated to check for slope of condensate line</td>
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The minimum current good manufacturing practice (CGMP) requirements for preparation of finished human drug products are described in 21CFR 211. These include the use of suitable protective apparel (21CFR 211.28), appropriate facility design and placement of equipment (21CFR 211.42), equipment cleaning and maintenance (21CFR 211.67), and production and process controls (21CFR 211.100).

Source: Case Studies of Microbial Contamination in Biologic Product Manufacturing | American Pharmaceutical Review - The Review of American Pharmaceutical Business & Technology
## Closed Bioprocess and Bioburden control

### General Comments

<table>
<thead>
<tr>
<th>General</th>
<th>Specific &amp; Relevant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understand the microbial entry points</td>
<td>Closed systems “block” microbial entry</td>
</tr>
<tr>
<td>Appropriate design of facility and equipment</td>
<td>Single-use systems and automation offer flexibility to facility design with ballroom concept, eliminating risks of contamination from personnel, material, waste handling</td>
</tr>
<tr>
<td>Validated cleaning and sterilization cycles for equipment</td>
<td>Single-use systems eliminate this requirement. Sterilization is only necessary for high-risk operations, such at and post final sterilizing grade filter.</td>
</tr>
<tr>
<td>Measures to reduce bioburden and bacterial endotoxins at appropriate steps in the process</td>
<td>Bioburden and endotoxin controls for raw materials and equipment. Principles of practice are the same for single-use, closed and continuous processes.</td>
</tr>
<tr>
<td>Routine monitoring of these process steps for bioburden and endotoxin with defined alert and action limits.</td>
<td>Same principles of practice</td>
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Source: Case Studies of Microbial Contamination in Biologic Product Manufacturing | American Pharmaceutical Review - The Review of American Pharmaceutical Business & Technology
Closed bioprocess and Bioburden Control
Focus on Chromatography – Questions/Answers

Q: What about chromatography columns, in terms of microbial contamination?

A: The columns, once packed, are closed. Storage and sanitization solutions which mitigate microbial contamination have been well-studied and implemented for years.

Q: What about sterilizing pre-packed chromatography columns by irradiation (e.g. gamma, X-ray, ebeam)?

A: Avoid manipulations that will cause chemical damage to the column, which has the potential to negatively impact the function of the column separation. I would track all specifications and be wary of any changes, even within acceptable ranges.

Q: What about gamma irradiation of single-use systems?

A: These polymeric materials have been studied more extensively by the medical device industry and their function may not be correlated to chemical properties but more physical characteristics. Even in the medical device industry, incidents regarding needle bonding adhesives and PVC material chemical changes have been detrimental.

PROPOSAL:
Avoid irradiation exposure for all chromatography resins and membranes.

• Risk of affecting chemistries and affinity ligands far outweigh benefits of sterilization.
• Experts highlight that "principles of practice" for chromatography bioburden controls have not changed.
04
mAb continuous processing technologies
Next Generation Processing

Evolution: Batch → Intensified → Continuous

Operating Scale
- 2,000 L SUB operated in fed-batch mode
  - Single harvest with 2.5 day batch cycle
- 1,000 – 2,000 L SUB operated in perfusion mode
  - Continuous harvest for 20-30 days
  - Target flowrate of 1,000-2,000 L/day

Product Manager – Cindy Delagree

CASSE Summer 2021
## Risk Mitigation through Design – Focus on Bioburden

### Risks

| Static – the fluid flows (i.e. flushes) slowly or does not flow in sections of the system (i.e. dead leg) | Design system to be dynamic with fluid continually flowing, especially around valve junctions. Test for flow flush timing and worst-case conditions. |
| Bioburden generated during process itself, based on risk of upstream impact of cell culture media and host cell artifacts. | Bioburden reduction filter (0.2 um) to mitigate microbial entry point from upstream. Additional filters may be added within system, but not necessary. |
| Bioburden results from non-sterilized chromatography columns run for 20-30 days | Bind/elute (Protein A affinity chromatography) mitigates risk versus flow through. Chromatography columns undergo sanitization cycles. |
| Bioburden present in single-use system components | Pre-gamma irradiated |
| Human operator errors | Automated system |

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**Mobius® Multi Column Capture System**

CASSS Summer 2021
Continuous In-Line Virus Inactivation

Industry standard: 60 minute hold
Robust inactivation > 4 LRV
2 holding tanks required
Manual process

Continuous pH adjustment with dynamic hold
Eliminates large holding tanks
Automated
Enables continuous operation

Applicability dependent upon:
- Residence Time
- Virus inactivation kinetics
- Efficient incubation chamber design
Risk Mitigation through Design – Focus on Bioburden

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<th>Mitigation</th>
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<td>Design system to be dynamic with fluid continually flowing, especially around valve junctions. Test for flow flush timing and worst-case conditions.</td>
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<tr>
<td>Bioburden generated during process itself</td>
<td>Limited Risk – further downstream, low pH conditions</td>
</tr>
<tr>
<td>Bioburden present in single-use system components</td>
<td>Pre-gamma irradiated</td>
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<tr>
<td>Human operator errors</td>
<td>Training and instructions for specific inputs, along with automated system controls</td>
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Regulatory Acceptance
Application Testing Strategy – 3 Pillars

❖ **Viral Inactivation Performance**
  • In-line performance robustly meets ASTM 2888 Standard (30-60 min residence time)
  • Inactivation kinetic studies to support short duration hold (~10 min)
  • Comparability of batch and in-line kinetics (batch performance predictive of in-line) + product quality attributes

❖ **Incubation Chamber Efficiency**
  • Chamber design for robust, reproducible, and predictable performance
  • Safety factor analysis to “guarantee” 5+ LRV
  • Scalability from bench to commercial scale to support validation studies
Viral clearance filtration – QbD and Validation
In-Line Spiking: Viral Clearance Validation for Continuous Processing

Key considerations -

- Sequential unit operations are started before the previous steps are completed.
- Virus filter or other clearance step sees variable operating feed parameters.

ICH Q5A - Measure virus removal using scaled down models that mirror large scale production to ensure that the virus removal results can be translated to the biotherapeutic product.

Source: Herb Lutz, MilliporeSigma
MilliporeSigma and MedImmune QbD collaboration – viral clearance filtration (Viresolve Pro)

- Resulted in the production of a knowledge package under QbD principles
  - Can be adopted by different users of Viresolve Pro and for different molecules
  - Addresses a previous gap in scientific understanding for regulatory filings
- In-house and vendor data can work synergistically to inform
  - Risk Assessments
  - Process characterization plans
  - Control strategy
- Cumulative (load volume and recovery flush) was identified as the only CPP for viral filtration – conservative approach
  - Based on mode of action
  - Need for additional project specific data to determine impact of amount load
  - Possibly downgraded after additional studies
- Knowledge package is very useful but does not preclude the implementation of in-house studies

Source: Herb Lutz, MilliporeSigma
Concluding Thoughts
Concluding Thoughts

Regulatory agencies...

• Are supportive of innovative biopharmaceutical manufacturing, including continuous manufacturing (CM). However, there is a lack of experience.

• Encourage the implementation of continuous manufacturing using a science and risk-based (QRM) approach.

• Recommend early and frequent discussions with Agency before implementation to ensure there is a mutual understanding.

• Highlight that current regulatory framework is adequate to allow CM (ICH Q7, Q8, Q9, Q10, Q11, etc). ICH Q13 will harmonize definitions and make things more efficient, but existing guidelines are supportive.

• Expect a level of detail and understanding about control strategy based on the risk.
Acknowledgements

MilliporeSigma Colleagues:
Ushma Mehta – Regulatory Consultant
Herb Lutz – Thought Leader Expert
Cindy Delagree – Product Manager
Thank You