Regulatory Perspective on New Developments in Manufacture of Biological Products

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Continuous and Advances in Manufacturing – Downstream

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Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA’s views or policies.
Outline

• Regulatory Framework for biomanufacturing
• Current state: Bulk Drug Substance
• New developments
• Regulatory perspectives: Product quality microbiology
• Conclusions
REGULATORY FRAMEWORK
Pharmaceutical CGMP for the 21st Century - A Risk Based Approach

• Initiative launched in 2002 to modernize FDA’s regulation of pharmaceutical quality of drugs intended to promote a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight
  – Intended to encourage the adoption of modern and innovative manufacturing technologies
  – Overarching philosophy is:
    • Quality should be built into the product, and testing alone cannot be relied on to ensure product quality
PAT- A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

• Guidance issued in 2004 defines Process Analytical Technology (PAT) as:
  – “a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical and performance attributes of raw and in-process materials and processes”.

• Overarching goal of PAT is ensuring product quality: “quality cannot be tested into products”

http://www.fda.gov/cvm/guidance/published.html
Need for New Initiatives

• FDA has been confronted with drug shortages and product recalls in the US at unprecedented rates in recent years.
  – These problems reflect deficiencies in pharmaceutical quality and manufacturing (outdated manufacturing technologies, facilities and equipment).
Testimony cited need to “modernize manufacturing methods by taking advantage of advances in modern facility and process design, such as replacing manually-intensive processes with automation, using closed systems, integrating process analytical technologies into operations for better process control, and adopting continuous manufacturing platforms. These technologies would help achieve improved manufacturing reliability, increased robustness, and lowered costs.”

Janet Woodcock, M.D., CDER Center Director
Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base

• In 2015 this draft Guidance was issued – to promote the modernization of manufacturing technologies which allow for more robust manufacturing process with fewer interruptions in production, fewer product failures and greater assurance for product meeting expected quality and clinical performance attributes.

• This guidance encourages companies to submit pre-submission questions and proposals to the FDA about the use of specific emerging technology to an Emerging Technology Team (ETT).
Adoption of new emerging technologies

- The biopharmaceutical industry is undergoing a paradigm shift in adopting new technologies in manufacturing.

- Bulk drug substance:
  - Continuous biomanufacturing
  - Single-use systems
  - Process Analytical Technology

A microbiologist’s perspective of the
CURRENT STATE OF BIOMANUFACTURING
Susceptibility to Microbial Contamination

- Biotech processes and products are prone to microbial contamination.
  - Products are heat-labile and cannot be terminally sterilized.
  - Raw materials, personnel and the manufacturing environment are a source of bioburden, endotoxin and other adventitious agents.
  - Products, process intermediates/pools, and raw materials support microbial growth.
- Each QA investigation for an over action bioburden limit can cost up to 20,000 USD and a failed batch up to 1 million USD (*Bioprocess International* vol. 15 (7), 2017)
Traditional Biopharmaceutical Facilities

• Large complex costly facilities
  – Designed to minimize contamination and cross contamination
    • HVAC systems for filtered air, stringent area classifications and segregation of functions based on contamination and cross contamination risks
  – Large and complex WFI systems
    • For large scale operation with high quality water demands
  – Complex CIP and SIP support systems
    • Extensive stainless steel piping aqueous process transfers
  – Large footprint for equipment and storage
  – Extensive maintenance programs, subject to frequent breakdown and contamination
  – Environmental monitoring
Traditional Biopharmaceutical Equipment

- Complex stainless steel vessels/bioreactors/hold tanks with gaskets, O-rings, valves
  - Batch bioreactors typically 10-20K scale
- Fixed, non-portable
- Connected to extensive stainless steel piping
- Subject to extreme temperatures, harsh chemicals during CIP or SIP
- Susceptible to wear, tear, breakdown
  - microbial contamination
Traditional Biopharmaceutical Manufacturing

• Limited output at the cell culture phase
  – Large stainless steel bioreactors for low yielding cultures at low cell densities
  – Very expensive and inefficient process
  – Use of animal derived products, complex media, and high quality water (WFI)
Traditional purification process

- Batch process whereby product is captured and purified via a large chromatography column.
  - Process supported by extensive validation activities.
    - Numerous hold steps after each column in stainless steel vessels that have undergone validated CIP/SIP cycles prior to use
    - Open operations (column packing and unpacking)
    - Microbial control is challenging
  - Process expansion is challenging (e.g., switching to larger columns is challenging).
  - Chromatography resins are typically underutilized because they are not loaded to their fullest capacity to avoid product breakthrough.
Bulk drug substance

NEW DEVELOPMENTS
New development in biomanufacturing

• Use of single-use-systems (SUS)

• Continuous biomanufacturing
  – Continuous perfusion systems with high cell densities, high yielding expression systems, prolonged manufacturing with disposable SUS
  – Simplification of harvesting steps
  – Continuous disposable multicolumn chromatography systems

• Use of PAT
Common uses of single use systems in Biotech manufacturing

• Buffer/media preparation
  – Sterile bags and connectors

• Seed expansion
  – Disposable rocking sterile bag bioreactor, connectors and sensors (e.g., wave bags)

• Bioreactors for cell culture
  – Up to 2000 -3000 L scale

• Purification
  – Disposable chromatography columns

• Product holding
  – Sterile bags and connectors

• Sampling
  – Sterile bags with connectors for closed system sampling

• Single-use filtration systems
  – Sterile bags, filters, and connectors
  – Disposable depth filtration capsule systems
Single-Use-Systems (SUS): Advantages

• Simplified facility design with extensive use of SUS:
  – Closed systems with less stringent area classification requirements
  – Reduced gowning – reduced human contribution to contamination
  – No requirements for clean-in-place and sterilize-in-place systems
  – Supplied gamma irradiated
    • Bags with in-line filters for closed system processing
    • Reduced hold time validation and microbial monitoring
  – Rapid change over
  – Multiproduct production
  – Easily replicated for installation in different facilities for tech transfers

• From a regulatory perspective facilities that have implemented the use of SUS have seen significant improvements in microbial control.
  – Fewer deviations and failures due to bioburden
Challenges of using SUS in biomanufacturing

• Compatibility with biologics
  – Extractables, leachables, particulates
• Leaks
  – Introduced during manufacturing, shipping, handling
• Suppliers and interchangeability of components
  – Connectors from different suppliers
  – Supply chain activities – change notification
• Packaging
  – System integrity; testing methods
• Lack of guidance on the use
• Disposal
Recent 483 observation from pre-license inspections: inappropriate connectors

- Equipment used for manufacturing name drug substance and name drug product is not adequate in that some of the parts do not match the equipment specifications. Specifically:
  - A leakage in the y-connector to the BDS filter assembly tool place on 2/24/2014 and was traced to a loose connection between 1/4” tubing and a 3/8” Y-connector (deviation report # 102882). The 1/4” tubing was used to fit the peristaltic pump. SOP-XXX-YYYY was updated (change control #101953) to replace the 1/4” tubing for a 5/16” tubing. However, the 5/6” tubing is not the right fit for the 3/8” Y-connector.

**Issue:**

Supplier limitations for spare parts; connectors from different suppliers are not interchangeable resulting in leaks during manufacturing; lack of integrity testing before use in manufacturing.
Continuous Manufacturing

- Konstantinov and Cooney (2014) in a White Paper on Continuous Bioprocessing described four examples of continuous manufacturing (three hybrid and one fully integrated):
  - Continuous upstream with batch downstream
    - Commonly used for complex and labile proteins
  - Batch upstream with continuous downstream
    - One or more downstream unit of operations are converted into a continuous operation
      - Examples: precipitation, flow-through purification, directly coupled chromatography columns without hold vessels
  - Continuous bioreactor and capture followed by batch downstream
    - Described by Warikoo et al. 2012
  - Fully Integrated continuous process
    - Not available at commercial scale yet
Continuous manufacturing: What is next?

• Integration of both upstream and downstream operations:
  – Continuous processing from the bioreactor to purification
  – Continuous chromatography steps

• **This approach is fully encouraged by the FDA:**
  – Support provided in presentations by FDA personnel
    • FDA 2011. Advancing regulatory science at FDA – A strategic plan. August (http://www.fda.gov/regulatoryscience)
    • Godwin 2011. Continuous manufacturing, a regulatory perspective. Interphex, New York, March
Integrated continuous manufacturing

• Warikoo et al. in 2012 described an integrated continuous manufacturing process for both a monoclonal antibody and a therapeutic protein:
  – A capture column connected to a bioreactor
  – The harvest from the bioreactor through a cell retention device (e.g., ATF) is pumped into a 2 L disposable bag serving as a surge vessel
    • Centrifugation step is eliminated
  – The harvest passes through a 0.2 µm filter and is loaded onto a capture column
  – Continuous operation at the capture step using multiple columns operated in series

Load first capture column with harvest

UV detector signal increases above threshold
Valve switch: Load second capture column with harvest
Elute first capture column with elution buffer
Collect eluate in vessel

UV detector signal increases above threshold
Valve switch: Load third capture column with harvest
Elute second capture column with elution buffer
Clean & equilibrate first column
Integrated continuous manufacturing: Benefits

• Improved process efficiency during purification:
  – More efficient utilization of chromatography resins
  – Decreased buffer usage
  – Reduced column sizes
  – Disposable columns

• Regulatory perspective
  – Use of closed system with improved microbial control
  – No hold times in vessels susceptible to microbial ingress and product contamination
  – No CIP or SIP validation
  – Reduced column cleaning sanitization and storage validation
  – Overall reduced microbial monitoring
    • Reduced sampling and testing
Use of PAT in continuous manufacturing

• Allows for a high degree of automation
  – Reduces human interactions for measurements and provides for greater process consistency.
  – Example (from Warikoo et al. 2012)
    • In-line measurement of product concentration with feedback control for column switching strategy using dynamic UV monitoring.
    • \( \Delta \text{UV} \) absorbance between the feed inlet and column outlet
      – Increase in UV absorbance in the outlet above impurity baseline triggers the column flow from one column to a second column in the series.

• Microbial monitoring is still conducted off line.

Bulk drug substance

FDA COMMENTS TO PROPOSALS
Segregation: Upstream/Downstream Pre-/Post- Viral Filtration

• Risk Assessments for viral contamination focus on the adequacy of closure of systems
  – SU bioreactors
  – SU bags
  – aseptic connections

• Risk Assessments lack important considerations:
  – Supplier Qualification for Aseptic Connections
  – Mitigation plans: leaks
  – Mitigation/responses to catastrophic failures
  – Inability to detect contamination in downstream processing steps
Upstream/Downstream Operations in CNC Rooms or ISO-9 with Reduced EM

• Closure risk assessment is not sufficient to justify use of ISO-9 or CNC rooms
  – Leaks present increased risk to the entire downstream process
  – Difficult to understand the root cause of contaminations/excursions without EM data
  – Failures of aseptic connections in ISO-9/CNC areas will lead to contamination
Multi-use/product Equipment Cleaning

• All hybrid traditional/CM and CM proposals have used some type of traditional equipment
• Potential sources of contamination:
  – Bioburden reduction/viral Filter changes
  – Centrifuge discharge
  – UF/DF membrane exchanges
  – Chromatography resin pack/unpack
• ISO-9/CNC environments pose increased risk for the above operations
Unanticipated Holds

- In connected operations, unanticipated holds are bottlenecks
- Deviation from validated process
  - Is there PQ impact?
  - Do upstream process pools/intermediates need to be discarded?
  - Is it possible to build unanticipated holds into the validation strategy?
Leak Isolation

- How will you identify leaks?
- What are your procedures to isolate leaks?
- What are your procedures to remove leaks?
- How will you determine if there is impact to downstream steps
  - Chromatography Resins
  - UF/DF membranes
Segregation: Clinical/Commercial Operations

• Clinical Operations, Development Products
  – Little/No FDA inspection history
  – Shorter manufacturing history
  – Microbiological limits may be unknown or non-existent
  – Microbial Contamination may not be investigated 
  \textit{by procedure}
Approaches to Biologics Manufacturing

• Traditional Approaches:
  – Open processing
  – Aseptic connections
  – Large complex facilities
  – Stainless steel tanks, bioreactors
  – CIP/SIP systems
  – Manually intensive
  – Inefficient
  – Extensive monitoring
  – Extensive regulatory oversight
  – Vulnerable to manufacturing disruptions leading to shortages

• New Approaches:
  – Closed processing
  – Single use systems
  – Continuous manufacturing
  – Process intensification
  – Simple facilities
  – Integration/automation (robotics)
  – Use of Advanced Analytics
  – Improved microbial control
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