Table 12: Continuous Manufacturing for Biologics

Facilitator: Yoen Joo Kim, *AstraZeneca*
Scribe: Allison Wolf, *Eli Lilly and Company*

Key Words:

Continuous manufacturing, ICH Q13, Single unit operation

Scope:

Continuous manufacturing approaches have been successfully implemented for small molecule manufacturing processes, which led to an FDA draft guidance in February 2019. This FDA guidance does not address biologics, but continuous manufacturing approaches are now starting to emerge for biologics. ICH Q13, Continuous Manufacturing of Drug Substances and Drug Products, was adopted in November 2022 and includes therapeutic proteins in the scope of the guidance with an Annex dedicated to control strategy and process validation considerations for therapeutic proteins. Recently, EMA announced the establishment of a Quality Innovation Expert Group that will include continuous manufacturing of biologics in their initial scope of work. While continuous manufacturing approaches have been used in the manufacture of biologics for a single unit operation (e.g., perfusion bioreactor), the application to unit operations such as Protein A capture chromatography may provide some efficiencies and allow for increased production without duplicate equipment sets or lengthy manufacturing times. This round table will discuss some of the opportunities for the use of continuous manufacturing approaches in the production of biologics and speak to potential challenges these approaches introduce.

Questions for Discussion:

1. Describe the current state of continuous manufacturing for biologics. Discuss technical limitations and challenges that may prevent implementation of continuous manufacturing for biologics.

2. Discuss solutions to these limitations and challenges, and emphasize key areas for technology investment or mitigation strategies for adoption of continuous manufacturing in the commercial sector.

3. Reflect lessons learned from continuous manufacturing for biologics. Discuss opportunities for collaboration across academia, industry and regulatory agencies to accelerate the development and adoption of continuous manufacturing for biologics.

4. Consider business challenges and regulatory hurdles that may impact the ability or the decision for industry to adopt continuous manufacturing processes.

5. Discuss any interactions with regulators regarding the implementation of continuous manufacturing for biologics.

Discussion Notes:

This roundtable included representatives from industry, regulatory agencies, and vendors who specialize in continuous manufacturing (CM) or PAT. Many of the industry participants are trying to change one or more unit operations to continuous. The discussion was robust and key discussion points are summarized below:

a. Regulator experience: Some sponsors want to make a product by two processes and release both to market at the same time, which has some challenges. Some of these situations are driven by a desire for efficiency and smaller modular footprints. It can be very challenging to switching over to CM for commercial products as this change (i.e., batch process to continuous) is considered a major process change. It is easier to implement CM at initial development/licensure. It is difficult to assess risk and impact of this type of process change for a complex biologic. Some sponsors have been successful, but they faced a high technical/comparability hurdle.
b. Current State of CM for Biologics: Perfusion bioreactor processes are one mode of CM that industry is using. Most of the manufacturing experience with new products used perfusion from the start as it is likely difficult to change from fed batch to perfusion bioreactor. Doing some individual unit operations in continuous manufacturing mode allows for much faster and smaller equipment train, which is a primary driver for implementing CM approaches. These gains in throughput have the potential to reduce manufacturing costs, which is another primary driver.
c. Industry experience: One sponsor saw a slight offset in potency results (~5%) so had some regulatory challenges associated with their change to CM. They discussed if/when clinical data may be needed to enable the change with such a slight offset in values. The clinical group at FDA will be concerned about a small change that is statistically meaningful and there isn't data/experience to know that there will be no impact to patients. This sponsor built a model linking levels of a specific product variant to clinical outcomes to support a lack of impact to patients.
d. Challenges with CM:
    i. How challenging is it for the agencies to review the technical/digital/PAT aspects of CM? One regulator concern is about control strategy to support combining small sections of a batch that may not be homogeneous and you dilute the difference. Complex biologics may never get to continuous manufacturing in the sense that small molecules are doing with plug flow reactors and full reliance on online measurement. Additionally for a biologic, you still need to define a batch for each unit operation and potentially link to a single vial thaw.
    ii. Use of PAT is common for biologics, but perhaps not able to do real time release testing with PAT. One recommendation is to pick the best point in the process to perform the testing so may not all be at final DS/DP testing. PAT may give you some of these testing results. Some manufacturers are using multi-attribute methods (MAM) on in process samples for process monitoring, but not using it as a batch release test in a QC laboratory.
e. Some sponsors have engaged with FDA's Emerging Technology Team (ETT) on CM approaches. At the end of the day, a continuous manufacturing GMP facility is not much different from a fed batch facility. Where it is different is that you may have more variety in surge vessels in terms of volume and hold times, etc. Some companies/manufacturers have built their CM platform using their own cell line.