独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

Points to Consider in Continuous Manufacturing of Biotechnological Products

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Specialized teams for CM at FDA, EMA and PMDA

US FDA

- ✓ Emerging Technology Team (ETT)
- ✓ Quality Considerations for Continuous Manufacturing;Draft Guidance for Industry

EMA

- ✓ Process Analytical Technology (PAT) team

PMDA

- ✓ Innovative Manufacturing Technology Working Group (IMT-WG)
- ✓ Consultation meetings, review(6 products approved), inspection
- ✓ AMED research group for small molecule
  - Study on quality assurance of pharmaceutical CM
- ✓ AMED research group for large molecule
  - Study on quality control strategies for the practical application of CM of biopharmaceuticals

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AMED: Japan Agency for Medical Research and Development

AMED research group for large molecule

- AMED funded research project
  - Studies on quality control strategies for the practical application of CM of biopharmaceuticals (May 2018 to Mar 2021)

    Project leader : Dr. Akiko Ishii-Watabe (NIHS)

    ◆Establishment of regulatory recommendations for CM

    Researcher : Shinichi Okudaira (PMDA)
- Research
  - Formed WG for Continuous manufacturing of biotechnological pharmaceuticals to work on paper showing regulatory considerations as Points to Consider document

    WG: PMDA, NIHS, PDA, JPMA, Osaka Univ, Kobe Univ, Gifu Phrm Univ, MAB

    Observed by AMED, MHLW, METI
  - Gathered information for the document, discussion with US FDA, site visit

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PDA Journal of GMP and Validation in Japan Vol. 23, No. 1, p13-22 (2021)

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Scope

Biotechnological products manufactured by applying the genetic recombination technology, in particular, antibodies developed by the method of QbD

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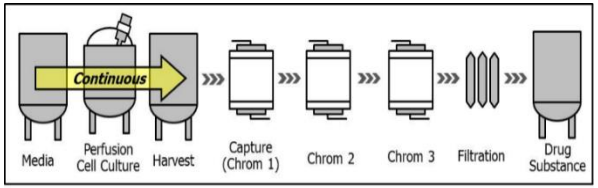
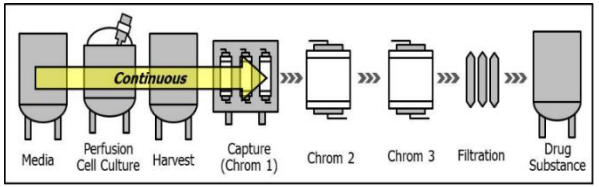
A model to discuss

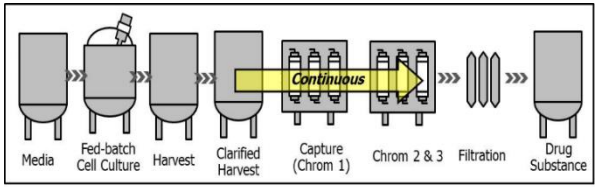
https://iscmp2014.mit.edu/white-papers/white-paper-4



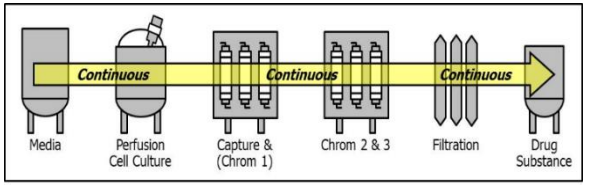
Example 1: Continuous upstream (perfusion), batch downstream



Example 3: Continuous upstream + capture, batch downstream



Example 2: Batch upstream, continuous downstream



Example 4: Continuous upstream and downstream

- A model in which certain parts of the culture and purification processes are continuous
- A model in which the culture process is continuous by perfusion culture, and that in which virus inactivation process is continuous

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Special considerations for CM of biotechnological products

As in small molecules,

- In order to ensure that products with the target quality are manufactured throughout the total operation time of the manufacturing processes in CM, it is necessary to not only control each manufacturing process independently but also to understand the dynamic characteristics between each unit operation, and for introduction of CM, it is necessary to establish a robust control strategy covering the whole manufacturing process and to demonstrate and maintain "State of Control“
- It is necessary to evaluate the impact of variation of process parameters (input variables) and process attributes (output variables) on the quality attributes of the products during the process development and to establish and execute an appropriate control strategy

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Special considerations for CM of biotechnological products

- Monitoring of product quality attributes and process attributes in manufacturing process
  - ✓ It is important to conduct manufacturing while confirming that the manufacturing process is operating under the intended conditions based on the monitoring of product quality attributes and process attributes over time, which is established at an appropriate stage and frequency
    - parameters related to the control of the cell separation in the perfusion culture process
    - parameters related to the use of a surge tank for adjustment of flow rate between the continuous processes
    - parameters related to multi-column chromatography
  - ✓ In the quality risk assessment for establishment of the control strategy, these process parameters need to be extracted appropriately, and the impact of their variation on CQA needs to be evaluated appropriately

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Special considerations for CM of biotechnological products

- Risk management associated with prolonged operation time
  - ✓ It is necessary to verify the long-term operation at the maximum scale in commercial production at the development stage or a later appropriate stage
  - ✓ When single-use products are used, it is necessary to control risks on the durability of materials, integrity of connections, and leachables, etc. in consideration of long operation time.

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Special considerations for CM of biotechnological products

- Methodology to achieve state of control in culture process
  - ✓ It is necessary to clarify in advance the relationship between the acceptable control range and affected quality attributes regarding the factors affecting product quality, such as culture medium components, culture environment, and cell status, to measure the factors in-line, on-line, at-line, or off-line, and to maintain the process in an appropriate state by feedback/feedforward control of the variations of the factors occurring during process operation

Examples of factors that may require control to achieve state of control in culture process

Culture medium components	Glucose, glutamine, glutamic acid, lactic acid, ammonium ion, other components, metabolites, etc. that affect the cell growth and the quality/yield of the desired product
Culture environment	Temperature, pH, dissolved oxygen concentration, dissolved carbon dioxide concentration, osmotic pressure
Cell condition	Viable cell density, growth rate, production rate of the desired product, cell viability

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Special considerations for CM of biotechnological products

- Process/equipment design that requires consideration of process dynamics
  - ✓ Evaluation of the impact on the quality is required for the residence time distribution (RTD) in the following processes.
    - RTD of the product in the perfusion culture device
    - RTD of the product in the continuous virus inactivation system and the composition, pH, and temperature distribution of the process liquid
    - RTD of the product in each column in a multi-column chromatography process
    - RTD of the product in a surge tank between processes

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Special considerations for CM of biotechnological products

- Start-up/shutdown
  - ✓ necessary to sufficiently examine the behavior of the manufacturing process at the start-up in advance and to verify in advance behavior to be observed and the acceptable range of variation
- Handling of deviations
  - ✓ an appropriate plan for rejection from the process based on an understanding of the process dynamics
  - ✓ a system to promptly investigate the when a deviation from the control range continues
- Definition of batch
  - ✓ not different from that in Batch Manufacturing and is as defined in ICH Q7 guideline

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Control strategy in CM of biotechnological products

- Establishment of control strategy for manufacturing process
  - ✓ Perfusion culture
    - Changes in the extraction amount of the product
    - Changes in post-translational modifications and impurities (host cell proteins, DNA, etc.)
    - Removal of excess cells, the bleeding frequency
    - Condition range that can maintain a state of control and to detect deviation early within the range of reversible change
    - The protein expression level, oligosaccharide profiles, etc. at the early, middle, and late stages of culture
  - ✓ Purification process
    - changes in the process dynamics of the components and product in the surge tank derived from the changes in the components of charged process liquid, changes in the charge-in/discharge flow rate, etc

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Control strategy in CM of biotechnological products

- Establishment of control strategy for manufacturing process
  - ✓ Understanding of process dynamics
    - It is important to identify the factors that affect the process dynamics and understand the mechanism and degree of the impact, because the process dynamics are a function of the material attributes of the raw materials, media, buffers, etc. to be charged in, design of the manufacturing equipment (stirring blades, sparger, etc. for culture equipment), biological reactions, separation reactions, process parameters, etc.
    - If CM equipment is stopped for any reason, mixing or contamination by passive diffusion may proceed even while the equipment is stopped
    - Device configuration so that virus is inactivated appropriately
    - For products manufactured using a platform method, the existing knowledge and experience on process dynamics may be used for other products.

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Control strategy in CM of biotechnological products

- Establishment of control strategy for manufacturing process
  - ✓ Understanding of material
    - Because raw materials are charged in continuously for a long time during manufacturing, there may be variations in raw materials, changes in the characteristics of the cells associated with prolongation of the culture period, or changes in the quality attributes of the target product (post-translational modifications, etc.). Raw materials and process conditions should be appropriately controlled to minimize the impact of the prolonged manufacturing period.
    - Critical quality attributes of raw materials that may affect process attributes or product quality attributes should be identified and acceptable control ranges should be established.
    - Cells used for manufacturing are particularly important among the raw materials

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Control strategy in CM of biotechnological products

- Establishment of control strategy for manufacturing process
  - ✓ Control strategy for quality risk/specific risk for CM
    - A control strategy against the risks associated with prolonged operation of processes and simultaneous operation of multiple systems
    - Process development using a systematic approach based on QbD is important.
    - In addition to the manufacturing knowledge and experience obtained during the development stage, it is important to systematically evaluate the manufacturing process, identify product CQA and affected critical process parameter (CPP), and weight controls according to the impact on the product quality.
    - An effective control strategy for Continuous Manufacturing should focus on reduction of potential risks that may cause process parameter variations affecting the product quality

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Control strategy in CM of biotechnological products

- Establishment of control strategy for manufacturing process
  - ✓ Control of adventitious agents in CM
    - For assurance of viral safety in the control of adventitious agents, ICH Q5A guideline can be used as a reference as in Batch Manufacturing
    - No difference in the contents to be considered for the control of cell lines and other raw materials between Batch Manufacturing and Continuous Manufacturing
    - For viral clearance tests, it is important to establish an appropriate model that reflects the commercial production, taking into account the principle and characteristics of the manufacturing equipment and if necessary, the influence of process dynamics
    - The basic concept of the stages when adventitious virus testing, etc. should be conducted is the same as that for Batch Manufacturing, but the necessity of sampling and the method should be considered in the design stage of the manufacturing equipment.

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Control strategy in CM of biotechnological products

- Process monitoring
  - ✓ Process monitoring and PAT
    - In CM, it is useful to assure the product quality by a real time measurement utilizing PAT. However, PAT is not matured to the level that can directly monitor the CQA in manufacturing of biopharmaceuticals, and the establishment of a method to determine the CQA in a timely manner is a technical challenge.
    - Multi-attribute method (MAM) is an expected technology of PAT, but there are many challenges for practical application.

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Control strategy in CM of biotechnological products

- Process monitoring
  - ✓ Process monitoring and PAT
    - In the culture process, if it is not possible to directly monitor the CQA of the product, critical factors such as the culture medium components, culture environment, and cell condition can be monitored in-line or on-line, in addition to general control items such as dissolved oxygen
    - In the purification process, the elution pattern by UV in the column chromatography process and characteristics of buffer solutions and process liquids in each process can be monitored as in Batch Manufacturing
    - In the virus inactivation process, process parameters (pH, detergent concentration, temperature, exposure time, etc.) to ensure the viral inactivation should be measured to confirm that the intended load was applied
    - In the virus removal filtration process, it is necessary to conduct the filter integrity test similarly in Batch Manufacturing

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Control strategy in CM of biotechnological products

- Process monitoring
  - ✓ Comprehensive quality attribute analysis method
    - One of the methods that is expected in the future as a technology for monitoring the quality of biopharmaceuticals in the manufacturing process is MAM, which comprehensively analyzes various quality attributes such as post-translational modifications
  - ✓ Points to consider for monitoring and sampling
    - Items used for the control of culture conditions should be monitored continuously, items related to the judgment of rejection from the process for non-conforming products should be monitored at a frequency in consideration of the range of rejection from the process, and items for confirmation of the process should be monitored at least once for each batch in consideration of the batch composition

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Control strategy in CM of biotechnological products

- Specifications and test methods
  - ✓ Concept of establishment of specifications and test methods
    - Common between Batch Manufacturing and CM
    - In cases where items monitored to check a state of control are within the control range and it cannot be denied that characteristic analysis items not specified may change even if the release test items are within the acceptance criteria, maintenance of the total level of quality control by adding appropriate items to the specifications and test methods can be a strategic option.
  - ✓ Challenges and risks in application of real-time release testing
    - At present, it cannot be said that RTRT is used even in Batch Manufacturing of biopharmaceuticals
    - There may be a situation where data cannot be obtained or the analytical performance is not sufficient because of a failure of equipment used for RTRT

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Process validation in CM of biotechnological products

- Process validation in Japan shall be conducted according to No.4 Validation guidance in “Partial Revision of Ministerial Ordinance on Good Manufacturing Practice for Drugs and Quasi-drugs" (PSEHB/CND Notification No. 0428-2 dated April 28, 2021)
- Various technical issues exist in the implementation of validation in CM. In particular, for the methodology to verify that products meeting the intended quality can be manufactured consistently along with the achievement of a state of control, there are various approaches as in Batch Manufacturing
  - ✓ Risks in Continuous Manufacturing equipment and methodology of qualification
  - ✓ Understanding of quality risk and concept of evaluation of process performance in Continuous Manufacturing
  - ✓ Concepts of application of process validation/continuous process verification

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Stability testing

- Concept for selection of primary batch
- Concept of the number of primary batches
  - ✓ stability evaluation according to ICH Q5C guideline is required.
  - ✓ it is necessary to understand quality attributes that may be affected during long-term storage in advance, taking into account findings obtained from accelerated testing, stress testing, etc., and to establish quality control strategies so that long-term stability is assured for the entire batch and products.

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Acknowledgment

Special thanks to WG members for CM of biotechnological pharmaceuticals
The research was supported by AMED (Grant Number JP20ae0101059)

Thank you for your attention!