



CONTINUOUS MANUFACTURING IN BIOLOGICS ADOPTION AND REGULATORY ENGAGEMENT

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❑ MANUFACTURING INNOVATION IN PHARMACEUTICAL INDUSTRY

❑ CONTINUOUS MANUFACTURING VERSUS BATCH PRODUCTION

❑ REGULATORY GUIDANCE IN CONTINUOUS MANUFACTURING

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MANUFACTURING INNOVATION IN PHARMACEUTICAL INDUSTRY

Industrial processes can be classified based on the process' output as:

☐ Batch processes

Batch process refers to a process consisting of a sequence of one or more steps that are performed in a defined order. A defined quantity of the product is produced at the end of the sequence which is repeated in order to produce another product batch.

☐ Continuous processes

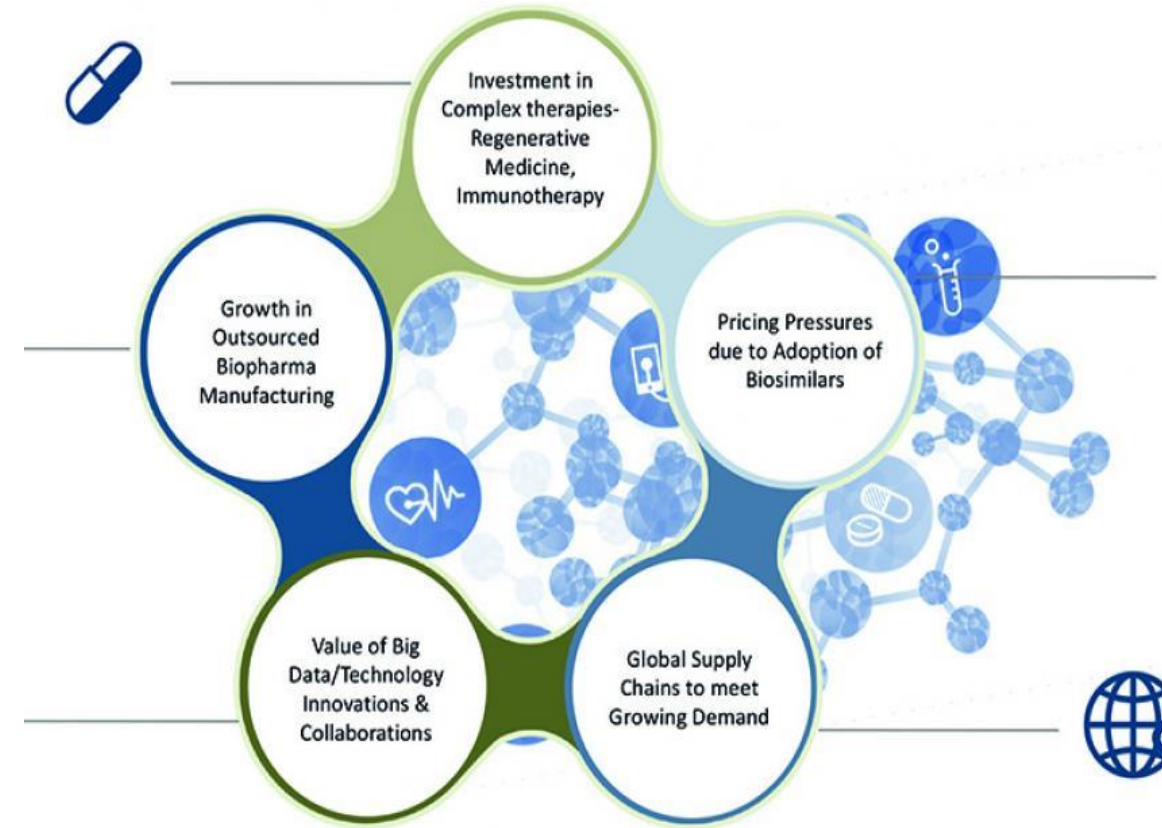
Continuous manufacturing (CM) integrates traditional step-wise manufacturing processes into a single system based on modern process monitoring and controls. In a CM process, product is made over time, so a drug manufacturer can easily control the amount of product being made to meet demand.

These efficient, integrated continuous systems also require smaller footprints to operate.



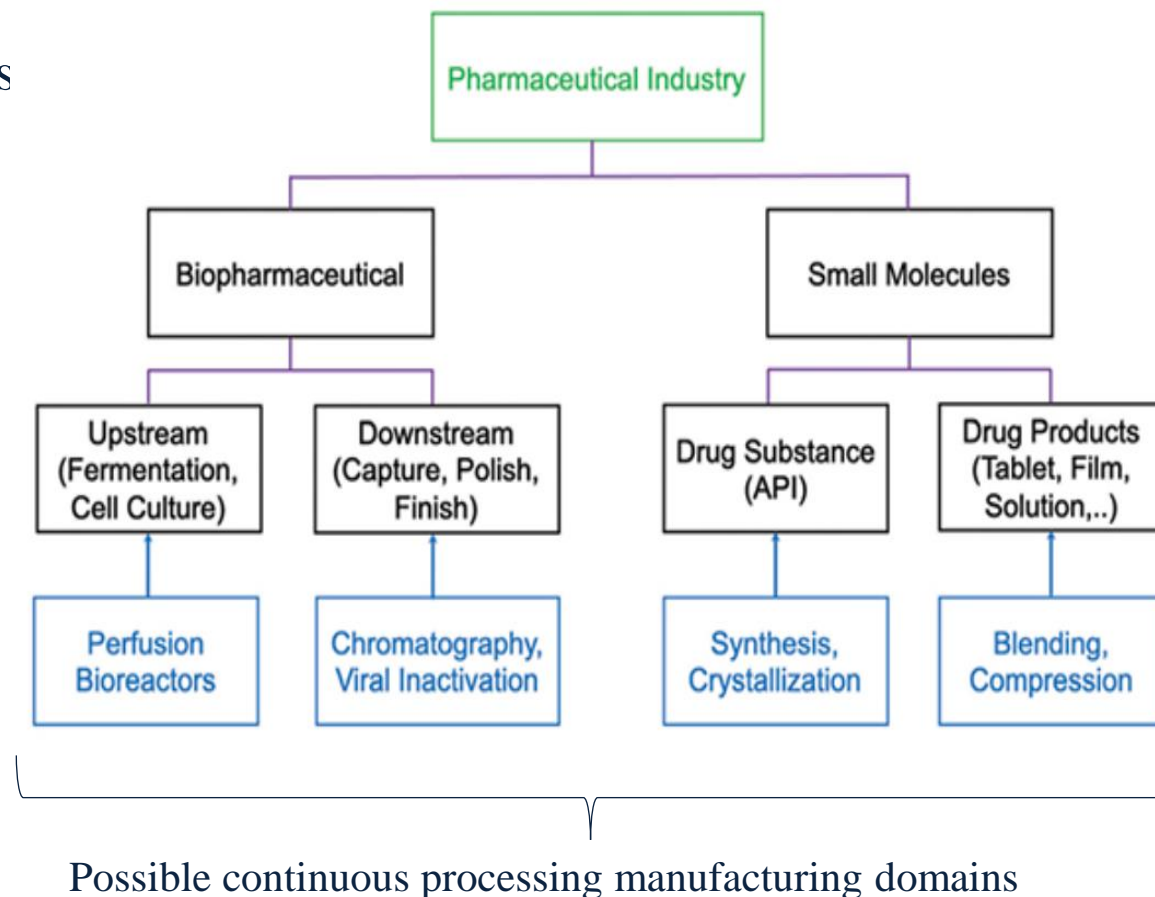
MANUFACTURING INNOVATION IN PHARMACEUTICAL INDUSTRY

- Integrating Novel Technological Approaches
 - Using established techniques **in a new or innovative way**
 - Applying production methods **in a new domain** where there are no defined best practices or experience
- New Manufacturing Technologies currently in progress:
 - Portable manufacturing units to respond to production on demand (POD's)
 - End-to end continuous manufacturing processing
 - Additive manufacturing (e.g. 3D printing)



WHAT IS CONTINUOUS MANUFACTURING ?

- ❑ **Continuous production** is a flow production method use to manufacture, produce, or process materials without interruption.
- ❑ **End-to-end Continuous Manufacturing** (according to FDA), is a **fully integrated process** in which raw materials or chemical intermediates are continuously fed into and transformed within the system (under continuous control and monitoring) and finished drug products are continuously removed from the system.
- ❑ Drug substance and drug product process steps are fully integrated into a single continuous system; testing and control are built into the system.
- ❑ The **hybrid approach** is a combination of batch and continuous processing steps. The pharmaceutical industry is increasingly adopting hybrid systems as it combines the advantages of batch and continuous processes.



BATCH PROCESS VERSUS CONTINUOUS PROCESS

- ❑ CM constitutes a direct translation of the unit operations contained on the process flow diagram.
- ❑ CM is based on the application of engineering solutions to create continuous flow and unit operation linkages, while conserving the underlying intent of the unit operations themselves as characteristic of fed-batch process.
- ❑ CM of API manufacturing is more complicated due to longer residence time, higher quantity and diversity of unit operations, and complexity of distinguished key molecules.
- ❑ Protein expression from either a fed-batch or continuous perfusion bioreactor utilizes the same cellular machinery in a conserved cell line.



BATCH PROCESS VERSUS CONTINUOUS PROCESS

	Batch Process	Continuous Process
Definition	Process that involves a sequence of steps followed in a specific order.	The flow of a single unit of product between every step of the process without any break in time, substance or extend.
Coordination	Scheduling is done to maintain the timing between move to earth.	Each machine performs a certain processing function and they operate in a steady state.
Quantities produced	A whole unit of products is produced.	Large quantities of products are obtained, greater ability to scale up
Process (cap)ability	Can be adapted to different products	Limited possibility to reconfigure the units operation Lower flexibility to accommodate different products per manufacturing line (minimize validation issues and the risk for contamination)
Cost of equipment	Low equipment cost	High equipment cost
Controlling	Batch process can be controlled very easily Batch release when testing is finalized and confirmed	Control batch process requires sophisticated, highly automated control systems Real time batch release
Shut Down times	Often	Rare
Workforce	Small workforce is needed	Continuous process is generally available in fully automated plants. If not, large workforce will be necessary.

CHALLENGES IN DEVELOPING CONTINUOUS MANUFACTURING IN BIOLOGICS

PRACTICAL CHALLENGES

- Raw material properties and variability
- Impurities and removal (degradation products accumulated over time)
- Viral safety and bioburden
- Material traceability
- Cell line stability and life span during a long fermentation process
- Product knowledge and structural/functional relationship
- Process, analytical control and control strategy, real time testing
- Design space and potential interactions between steps
- Evaluation of manufacturing changes and impact on product quality





CONTINUOUS MANUFACTURING PROGRESS

Medicine Products using continuous manufacturing process, approved on the market are

Small Molecules, solid oral dose drug products.

Drug	Pharma company	Indication	FDA	EMA	PMDA Japan
Daurismo	Pfizer	Acute Myeolocytic Leukemia	X		
Orkambi	Vertex Pharmaceuticals	Cystic Fibrosis	X	X	
Prezista	Johnson&Johnson	HIV	X		X
Symdeco/ Symkevi	Vertex Pharmaceuticals	Cystic Fibrosis	X	X	
Trikafta	Vertex Pharmaceuticals	Cystic Fibrosis	X		
Verzenio	Elli Lilly	Metastatic Breast Cancer	X		X

- In addition to technical challenges, there are also **regulatory challenges**, especially for implementation of CM in Biologics.

Current CM guidance:

ICH Q8-12: Product and process understanding and process control (ICH Q8)

Quality risk management (**ICH Q9**)

Quality systems (**ICH Q10**)

Development and manufacture of DS/ Quality by design (**ICH Q11**)

Lifecycle approach to process control/validation (**ICH Q12**)

Continuous Manufacturing of DS and DP covered by ICH Q13 – available
CM is consistent with EMA/FDA **quality by design (QbD) guidance**.

There is still limited experience on HA side with CM on Biologics.

- Industry and regulators need to collaborate and embrace innovation to advance and facilitate the implementation of CM in Biologics.



Variation	Description	Type (EU)
B.I.1.2 Change in manufacturing process of an API	c) The change refers to a biological/immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological substance, which may have a significant impact on the quality, safety and efficacy of the medicinal product and is not related to a protocol	II (major)
B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance	c) The change requires assessment of the comparability of a biological/immunological active substance	II (major)
B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance	d) Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological active substance	II (major)
B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product	c) The product is a biological/immunological medicinal product and the change requires an assessment of comparability	II (major)
B.II.b.4 Change in the batch size (including batch size ranges) of the finished product	c) The change requires assessment of the comparability of a biological/immunological medicinal product or the change in batch size requires a new bioequivalence study	II (major)

- ❑ The **science exists to enable continuous manufacturing** of pharmaceuticals. Specific scientific considerations related to sampling frequency for continuous manufacturing
- ❑ **FDA/EMA support the implementation** of continuous manufacturing using a science and risk-based approach. Recommend and supports early and frequent discussion with Agency before implementation
- ❑ **North America** is likely to be a **faster adopter of continuous manufacturing**. It is expected to hold dominance in the global market. Support from regulatory bodies, openness of leading pharmaceutical companies toward the latest technologies, and the mounting pressure on pharmaceutical companies to reduce operational costs will fuel the demand for continuous manufacturing in North America.



"I'm just waiting to see what you're making,
so I can write some regulations for it."

CONTINUOUS MANUFACTURING- REGULATORY ENGAGEMENT

- ☐ Interactions with different health authorities
- ☐ Interactions with other industry representatives to identify and discuss common challenges, seek alignment on industry position on CM implementation strategy



CONTINUOUS MANUFACTURING- SHAPING THE FUTURE

❑ To facilitate adoption and ensure global consistency:

-new regulatory guidelines and policies are needed to support the future state of ILM (in line monitoring)/RTR (real time release)

-facilitate submissions for new and existing products. Regulatory agencies need to be involved throughout the process to prevent issues resulting from missing or inconsistent guidelines.

❑ Regulatory agencies are supportive to innovative technologies, but are not globally harmonized, requirements may differ significantly, therefore, **global implementation is still a challenge**, complicating supply chains.



“We only have a few rules around here,
but we really enforce them.”

CONTINUOUS MANUFACTURING- SHAPING THE FUTURE

Significant engagement efforts between industry and regulators are ongoing and focus on:

- ❑ How to **ensure suitable and effective regulations and guidance** to facilitate faster implementation of new technologies and allow faster patient access to breakthrough therapies?
- ❑ How to **facilitate the implementation of CM** as a post approval submission for marketed products and allow **the option to use two manufacturing processes under one license** for a product, especially when global harmonization is still a challenge?



CONTINUOUS MANUFACTURING- SHAPING THE FUTURE

- ❑ Drugs in various pharmaceutical dosage forms using CM technology would likely be **approved** in the coming years
- ❑ **Regulatory harmonization** can be achieved through a large adoption of **ICH Guidelines**, as a main reference, by health authorities to provide:
 - better clarity** to the manufacturers on the regulatory requirements for global implementation
 - confidence** to invest and overcome challenges using a new technology by pharma companies
- ❑ **Implementation of ICH Q13** should limit significantly the hurdles of CM implementation



CONTINUOUS MANUFACTURING SHAPING THE FUTURE

- ❑ Commercial implementation is on the way. **Pharma industry and regulators work together** to support CM technology, engage in active discussions, building experience and facilitate implementation.
- ❑ Current regulations and guidance are supportive, nevertheless there are still challenges and specific technical aspects to be considered, therefore, **early and active engagement with authorities** is crucial in successful approval.
- ❑ **CM prepares pharma industry for the future**, using novel and flexible technologies to adapt, to meet therapeutic needs (e.g. personalized medicines), market changes and demand, and minimize the risks and costs.



*Thank
you*

