Master's Thesis
Degree Project in Pharmaceutical Technology - KLGM05

Quality and Regulatory Issues Related to Continuous Manufacturing of Biologics

By

Sorosh Ziarati

Department of Food Technology, Engineering and Nutrition
Faculty of Engineering, LTH, Lund University
SE-221 00 Lund, Sweden

Supervisor:
Lars Nilsson
Department of Food Technology
Lund University
Assistant supervisor:
William Mackintosh
Rise Institute, Stockholm
Examiner:
Marie Wahlgren
Department of Food Technology
Lund University

Printed in Sweden by Media-Tryck.
Lund 2022

Abstract

Introduction:
Continuous Manufacturing involves the continuous feeding of input materials into the transformation of in-process materials within, and the concomitant removal of output materials from a manufacturing process based on ICH guideline. In these systems, all the processes from raw material to final finished product would be continuously produced. The project aims to: Investigate the challenges and issues of producing a drug from API (Active Pharmaceutical Ingredient) to the final product using "*Continuous Manufacturing (CM)*".

Methods: In several interviews, with experts from pharmaceutical companies, information is gathered about the challenges which exist for them to transfer a production line from a batch-based system to a continuous manufacturing line. Moreover, a designed process would be chosen and a comparison study will compare the challenges of transferring the process to a continuous manufacturing while focusing on the regulation and GMP issues.

Results: It was concluded that from a regulatory point of view, authorities are welcome to any changes as long as the manufacturer could provide data that they have complete control on the process. However, it is harder for manufacturers to convince the authority for the conversion for their production line to CM compared to starting a new production line with CM systems.

Conclusion: It was conducted that converting batch systems to CM is not economically beneficial for manufacturers. Due to this reason CM system would be only beneficial when there is a high demand for a product or a new production line is going to be built.

Keywords: Continuous Manufacturing, Regulation, Continuous freeze drying, Biopharmaceutical, Trastuzumab.

Popular scientific summary

The pharmaceutical industry is one of the most important aspects of modern human society. This industry has allowed scientists to improve mankind's life and gives all patients around the world a hope to treat their disease. The pharmaceutical industry has not seen that much changes when it comes to production of small molecules and API for the past decades. However, the world is changing. New diseases, pandemics, and more demand around the world for drugs and treatment have been challenging the industry. Moreover, with the advancement within biotech and biopharmaceutical new technology are needed. In order for the industry to adapt itself with new demands and challenges, scientists have been researching and investigating new technology.

One of the areas which scientists have been investigating for the past years is increasing the production rate of companies' production lines. There are several ways to reach such a goal in order to increase the production rate to meet the demand of the public. This includes building new factories, having more working shifts in the factory and improving the production line to be more efficient. One of the ideas to improve the production rate of existing production lines is to convert existing systems to Continuous Manufacturing. Continuous Manufacturing is a mode of production which increases the production rate by compiling all units of operation in one. This action would allow the manufacturer to increase their production speed by lowering the time needed for transport, storage, and man power.

These systems would allow companies to produce more drugs and treatments in a shorter time, thus meeting the public demand in the case of drug shortage or pandemic. However, health authorities want to be sure that these systems are safe and would not harm patients by any chance. In this thesis the author is going to investigate the possibility of implementing these systems to produce biological drugs. This thesis focuses on interviewing professionals who work in pharmaceutical companies, to investigate challenges and problems to use Continuous Manufacturing. After designing a continuous process for production of trastuzumab which is used in the treatment of breast cancer, this designed process was presented to professionals for their opinion. It was understood from interviews that the CM system has some advantages in some parts of manufacturing which allow the industry to make their process safer for the patient. However, due to shortages in spare parts and implementing, these systems are not economically beneficial in a lot of cases. Due to this reason Continuous Manufacturing has not been implemented in a meaningful number around the world.

Popular scientific summary (Swedish)

Läkemedelsindustrin är en av de viktigaste aspekterna i det moderna samhället. Denna industri har tillåtit forskare att förbättra människans levnad och ger patienter världen över hopp att deras sjukdomar kan bli behandlade. Läkemedelsindustrin har inte sett så många förändringar när det kommer till produktioner av små molekyler och API under de senaste årtiondena. Men världen förändras. Nya sjukdomar, pandemier, och mer behov av läkemedel och behandlingar världen över har utmanat industrin. Dessutom, i samband med biotekniska och biofarmaceutiska framsteg, behövs ny teknologi. Forskare har, för att industrin ska kunna anpassa sig efter nya behov och utmaning, utforskat denna nya teknologin.

Ett av områdena som forskare har utforskat under de senare åren är utökning av produktionsnivån hos företags produktionslinje. Det finns flera sätt att nå ett sådant mål att öka produktionsnivån för att nå upp till allmänhetens behov, som att bygga nya fabriker, ha fler arbetsskift i fabriken, och att effektivisera produktionslinjen. En av idéerna för att förbättra produktionslinjen hos befintliga produktionslinjer är genom att konvertera befintliga system till kontinuerlig produktion. Kontinuerlig produktion är ett produktionssätt som förbättrar produktionsnivån genom att sammanställa alla driftsenheter till en enda. Detta skulle låta producenten öka produktionshastigheten genom att sänka tiden det krävs för transport, minska förvaring och minska arbetskraften som krävs.

Dessa system skulle tillåta företag att producera fler läkemedel och behandlingar på kortare tid, och därmed möta allmänhetens behov vid händelser av läkemedelsbrist eller pandemier. Hälsomyndigheter vill dock vara säkra på att dessa system är trygga utan risk för att skada patienter. I denna uppsatsen kommer författaren undersöka möjligheten att implementera dessa system för att producera biologiska läkemedel. Denna uppsats fokuserar på att intervjua professionella som jobbar inom farmaceutiska företag, för att undersöka utmaningar och problem med användningen av Kontinuerlig Produktion. Efter utformningen av en kontinuerligt process för produktion av trastuzumab, som används för att behandla bröstcancer, presenterades denna process för professionella för att få deras åsikt. I intervjuer framgick det att det Kontinuerliga produktionssystemet har vissa fördelar i vissa delar av produktionen, vilket tillåter industrin att göra deras process säkrare för patienten. På grund av brist på reservdelar blir dock dessa system inte ekonomiskt fördelaktiga i många fall. På grund av denna anledningen har Kontinuerlig Produktion inte implementeras i speciellt stor utsträckning världen över.

Acknowledgments

This master thesis was a unique opportunity for me to improve my knowledge on the pharmaceutical industry. During this thesis I had the opportunity to meet professionals from around the world, talk with them and use their experience. During my master degree journey at Lund University I had the chance to learn about the pharmaceutical industry, make new friends, and meet new people who taught me valuable things.

Lars Nilsson, my supervisor, thanks for supporting me and letting me follow my interest during my thesis and studies. Thanks for all the help and supporting me during this time.

William Mackintosh, my assistant supervisor, thanks for all the support during my thesis studies. Thanks for all the help during this time, your dedication and all your effort, your perspective and insight from the industry.

Ruxandra Ionescu from Propharma group, thank you for your participation, offering your knowledge, input, and assistance during this project.

Sajal Patel and Irina Ramos from AstraZeneca, thank you for your participation, offering your knowledge, input, and assistance during this project.

Lovisa Ringstad from Ilya Pharma, thank you for your participation, offering your knowledge, input, and assistance during this project.

Newsha Mirzaie and Patrick Aurenz, thanks for the help, support, and efficient assistance during this study regarding economical guidance.

Parsa Rostami and Albin Edvardsson, thanks for being such caring friends. Thanks for all the support during my thesis.

Table of contents

Abbreviations and symbols

API	Active Pharmaceutical ingredient
CM	Continuous Manufacturing
FDA	Food and Drug Administration
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human use.
HER2	Human epidermal growth factor receptor 2
ERBB2	Receptor tyrosine-protein kinase erbB-2
GMP	Good manufacturing practice
WHO	World Health Organization
SOP	standard operating procedure
CEX	Cation-exchange chromatography
AEX	Anion-exchange chromatography
CQA	Critical Quality Attribute CQA
EMA	European Medicines Agency
PQS	Pharmaceutical Quality Systems
IPC	In process control
CPP	Critical Process Parameters
IEX	Ion Exchange Chromatography

Objective

The project aims to:

- Investigate the challenges and issues of producing a drug from API (Active Pharmaceutical Ingredient) to the final product using "*Continuous Manufacturing (CM)*".
- Investigate the possibility and issues of transferring the mock batch system to a CM and determine the critical points in a mock system.
- Define the batch for a mockup process.
- Investigate possible quality and regulatory challenges using CM.

In order to reach the objective of this project, several interviews were conducted with professionals from different pharmaceutical companies. Moreover, the designed CM process was presented to professionals via the Next Bioform organized by RISE Institute in Stockholm. This project is expected to help, understand and overcome the regulatory and technical issues of continuous production systems. Moreover, it is expected that the outline of this project would help the regulatory officials, academia and companies to expand their production line and find how to implement these systems in their existing production line. Furthermore, by comparing and developing two similar mock systems, understanding the issues of converting the normal batch to CM systems would be achievable.

Background

Continuous Manufacturing is referred to as an integrated unit of the operating system. In these systems, all the processes from raw material to final finished product are continuously produced. There have been several advantages for adopting such a system in large production lines including the ability to use smaller size production lines. Owing to this factor, the size of the factory and the initial cost for building a production line will decrease. Moreover, CM could be the alternative answer for supply chain problems, shortages, or any emergency therapy in the future [1]. However, there have been several drawbacks for these systems. For instance, ensuring quality control through all produced batches, defining a batch and tracing them to the original material, ensuring that there wouldn't be any deviation or changes in API in the bioreactor in different batches. Since the Covid-19 pandemic in 2020 brought about manpower shortage and higher market demands for

medical products, medical treatment production is needed to be accelerated so as to meet the demand of the public needs. Thus, CM has been brought to attention as a next-generation production line for the pharmaceutical industry.

Introduction

Pharmaceutical Industry

The Pharmaceutical Industry can be determined as one of the biggest and fastest growing industries in the twenty-first century [2]. One of the aspects of this industry is biopharmaceutical which focuses on various fields such as antibody treatment, enzyme and cell therapy. During the past 50 years, little changes have occurred to the overall manufacturing process [1]. However, due to the limited nature of the current manufacturing capability, economical elements, and supply chain issues for APIs, it is not possible to meet the demands of the patients in the time of emergency or pandemics [3]. Thus, it is necessary to invest in a system which could improve the desired manufacturing speed. For the past 20 years, the aim of the industry has been changed to implementing CM systems in pharmaceutical [4].

Batch Process

As can be seen in figure 1, in a traditional or currently used batch system, the raw material would be introduced to the system despite the fact that the intermediate is discharged at the end of each stage. In the pharmaceutical industry, the terms “batch” and “CM” could be used for each individual unit of an operation or the entire manufacturing system. In the batch system, the uncompleted product would be transferred to a buffer stage and so as to be restored until it comes to the next step [5]. These buffers, also known as storage tanks, are designed so as to provide us with the opportunity for offline analysis. After analyzing, the material would be transferred to the next operational unit. Furthermore, in case of any malfunction or any mutation in the process, the material would be thrown away [5]. Comparing the batch with the CM system, it can be suggested that in the batch system has several advantages. For instance, the cost of operation and capital investment would be lower and the production of some treatments is only feasible by batch process owing to their complexity.

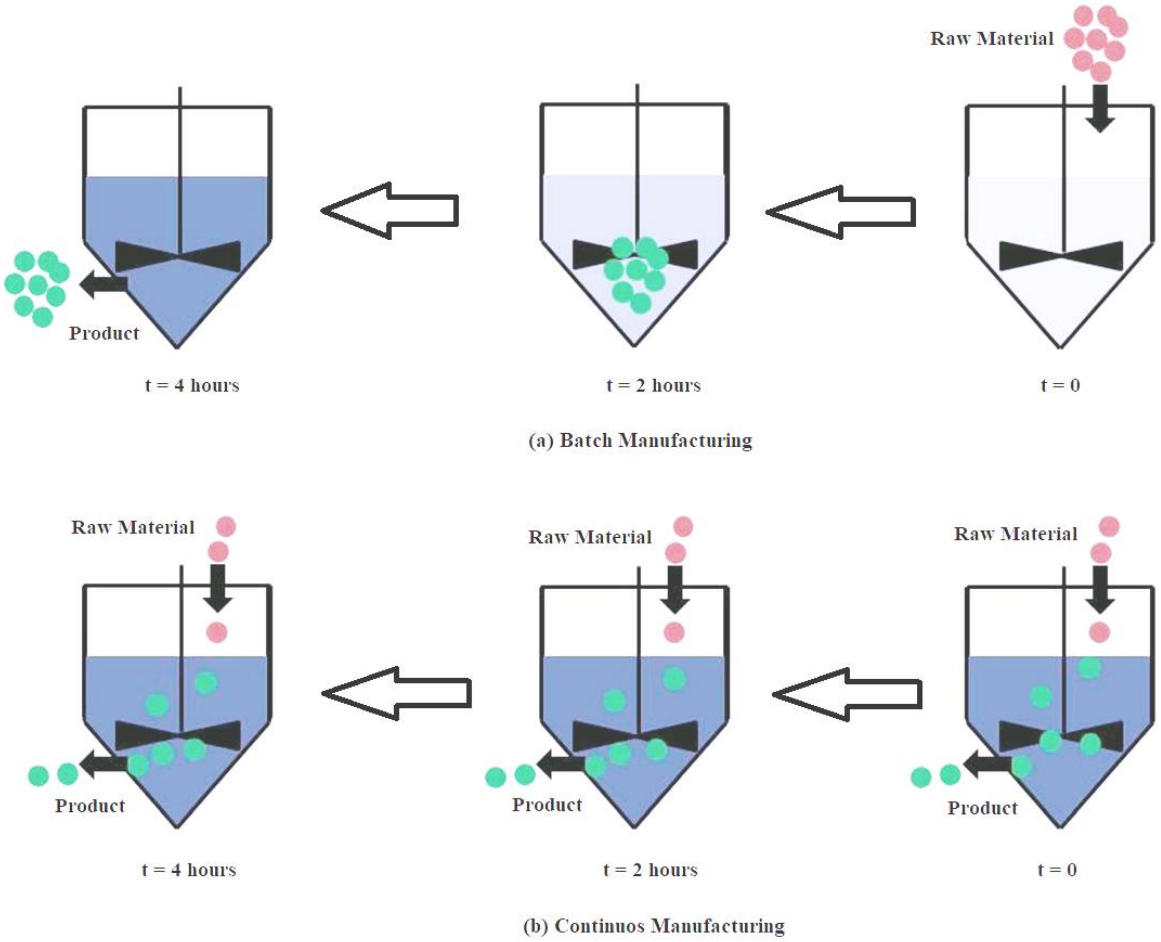

Figure 1. Illustrating time comparison between batch and CM systems [5]

Continuous Manufacturing

A CM system can be defined as a type of manufacturing where everything, starting from the raw material, would be continuously added to the process and the material would exit the system in the same way [6]. In recent years, the industry has changed its focus and is now investing more to study and implement the concept of CM in their production lines. Although CM is a new concept, there are already several production lines which have been converted to CM [6][7]. The first one approved by the FDA was in 2015 for Vertex's Orkambi (lumacaftor/ivacaftor) to treat cystic fibrosis [8]. Mainly there are already several ideas to implement the CM system in the production line. Based on the available infrastructures, the economic aspects, and the concept of the finished product, a CM system can be implemented in three ways based on the ICH Q13 guideline titled "Continuous manufacturing of drug substances and drug products", current version mentioned below.

1. It could be implemented on some of the operational units making the production line a hybrid system which includes batch and CM mode at the same time.
2. All units of operation in the manufacturing line are converted to CM and integrated in continuous mode.
3. A mode that all units of operations used in the drug substance and product would be integrated across the boundary between drug substance and drug product [9] [10].

As it has been mentioned, there are several advantages to convert the process from batch to CM including the following factors:

1. Smaller equipment is needed correspondingly to the size of the factory and equipment could be smaller than the usual batch system [1].
2. Lower cost of production.
3. Reduced safety hazards.
4. "Scale out" instead of scaling up [11].
5. The CM system could be used in the future to develop personalized medicine.
6. The CM could be used to produce the drug substance faster in the time of pandemics and emergencies [11] [1].

On the other hand, due to high costs of converting the existing production line to a CM system, regulatory challenges, technology problems, and quality and technical challenges, the industry has been hesitant to convert from batch system to CM. As illustrated in figure 2, the concept of CM would allow the manufacturers to start their new production line on a smaller scale compared to the batch system. Thus, the size of the factory and the manufacturing line could be reduced by up to 40 % [1][9]. In addition, the time needed to manufacture a treatment can be reduced from months to days due to efficacy, lower volume and higher input [5].

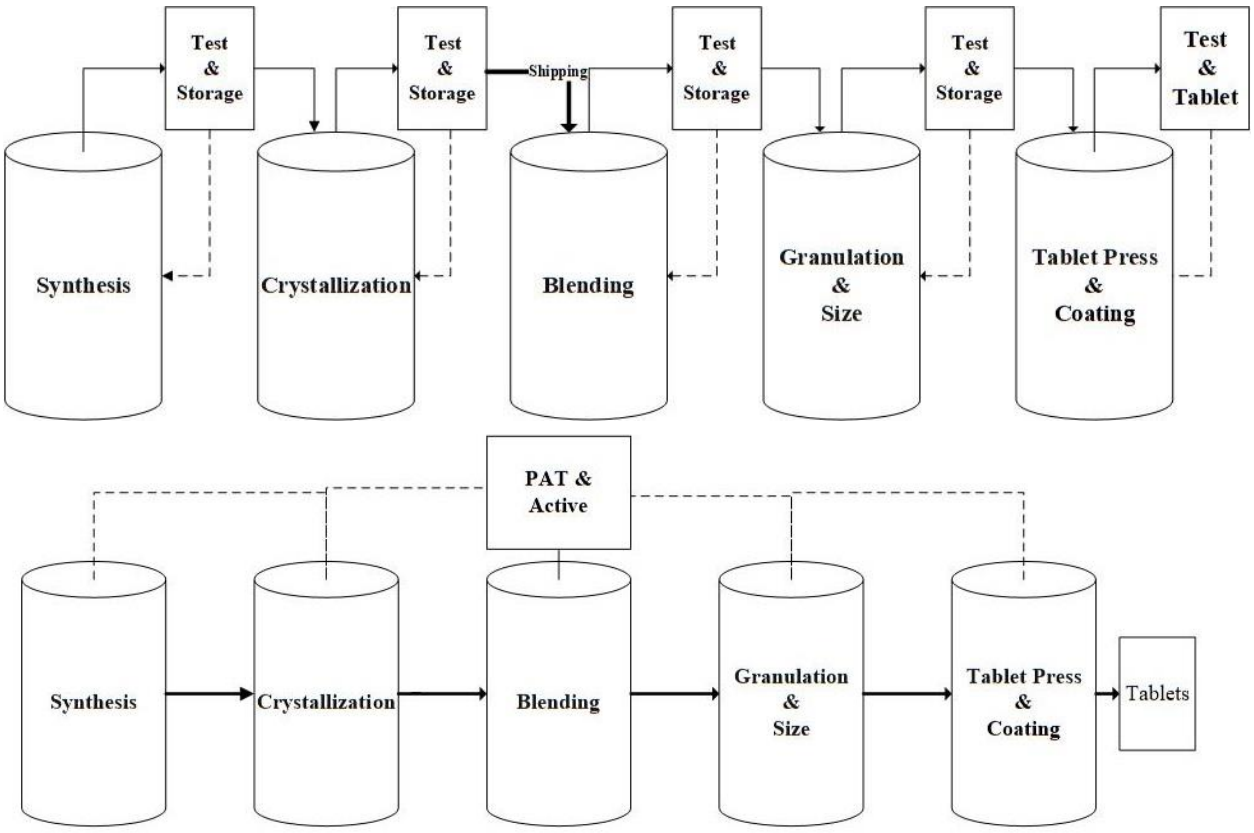

Figure 2. illustrating deference's between CM and batch system [5].

Regulation

The goal of all pharmaceutical companies is to develop and deliver their product without endangering their patients' lives. In order to achieve this goal, companies need the approval of the local health authority of the country of interest so as to be able to sell their treatment. In order to get the approval by the local health authorities according to requirements in that particular country, all the aspects of the process need to be approved by the government and legislation. Some of the most famous legislations are the rules of "*Food and Drug Administration (FDA)*" and the "*International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)*". The regulations differ in different parts of the world, also between FDA and EMA. In an attempt to align and harmonize the different requirements from different authorities, the ICH issues guidelines. These organizations exist to guarantee the safety and efficiency of different drugs produced. In order for companies to get the approval to sell their product, they need to provide information about all the aspects of their product, all clinical trials data, drug side

and main effects, "*Good Manufacturing Practice (GMP)*", and formulation and analytical process, for instance. This information is needed to represent the safety, efficacy and quality of the drug and to guarantee that the company meets all the current regulatory requirements and standards needed to sell their drug product [9] [10].

Regulation regarding continuous manufacturing

In order to encourage the industry to move toward the CM process and guarantee a safe product, authorities have released several guidelines for the CM process. These are the key guidelines for the concept of CM. However, the most important one could be ICH Q13. This guideline is issued to facilitate the use of CM for those who wish to use this procedure. In this guideline the authorizes view on continuous production is described. Key issues that are brought up are:

1. Control Strategy

The guideline suggests the control strategy in the case of CM is the same as the batch system. However, one aspect which is different and only unique to the CM system is the environment and process product condition which must be considered in more detail. In this section, the guideline gives some suggestions which are unique for CM. For instance, state of control, traceability, raw materials and intermediates, equipment, and material characterization and control [9] [10].

2. Process Development

As can be understood from this section, pharmaceutical companies can use different strategies to implement CM in their production line. Some of the examples on this are: hybrid, or fully continuous CM Similar to a batch system. All key designs and control systems should be described plus an overall general strategy. Some of the considerations which could be included for a CRM system are flow rate of material through the process, factors affecting "scale" of the continuous manufacturing, *"In Process Control(IPC)"* points and control systems integral to the control strategy [9] [10].

3. Regulatory Consideration

Based on the ICH guideline and FDA there are several categories which need to be considered. As Described in ICH Q13 and ICH M4Q there should be a description of the process available including technical information about the process. This information should go through operating conditions, a flow diagram, location of the unit operations,

detailed indications of the CM and batch process and critical points. Furthermore, there should be evidence to support that there is a working control system to ensure the safety of output material and traceability to input material [9] [13]. In addition, there should be a reliable process control and working monitoring system. There should be also evidence regarding maintaining the unit of operation. Another aspect which needs to be provided to the authorities is system operation, which means providing evidence that there are working procedures regarding all units of operation [13]. As can be seen in table 1, some of the important relevant ICH guideline examples for continuous manufacturing are mentioned [6].

Table 1. ICH guideline regrading continues manufacturing [6].

Number	Title	Contents of Relevance to CM
ICH Q8	Pharmaceutical Development	Continuous process verification
ICH Q9	Quality Risk Management	Risk assessment and control
ICH Q10	Pharmaceutical Quality System	process performance

4. Pharmaceutical Quality System and Conversion of batch process to CM

Based on the ICH Q13 there is no difference between batch and CM processes when it comes to *"Pharmaceutical Quality Systems (PQS)"* expectations. One important operational aspect of CM is that non-conforming materials can be diverted from the rest of the batch when material traceability, process monitoring, and material diversion strategies are well established. Based on Q13, companies just need to present evidence regarding control strategy. Furthermore, the quality of the finished product should be comparable to batch mode. Moreover, manufacturers also need to present bioequivalence, using non-clinical or clinical studies, as well as science and risk-based approaches for all processes within biologics [9] [10].

Trastuzumab

In this project, the manufacturing of *Trastuzumab* has been decided to be used as a case study. Trastuzumab is used as a cancer treatment on patients with "*human epidermal growth factor receptor 2 (HER2*)" positive. The HER2 is a receptor which can be found on the human cell surfaces. This receptor is encoded by the "*Receptor tyrosine-protein kinase erbB-2(ERBB2)*" gene. Cancer patients usually have more than 2 million of HER2 receptors on each individual cell [links below and FDA]. In contrast, healthy people usually have around two thousand HER2 receptors on their cell surface. This high number of HER2 is determined by multiple copies of ERBB2 genes in a patient's cancer cell as can be observed in figure 3 [14]. Trastuzumab is lyophilized powder which is known in the market as "*Herceptin*". It is used as monoclonal antibodies treatment for patients with breast cancer mainly used via injection [14]. Trastuzumab slows down the growth rate of cancer cells by attaching to HER2+ and blocking it causing intracellular signaling to stop [15]. The way that Trastuzumab is used is based on the chemotherapy treatment in a way that after two rounds of chemotherapy the monoclonal antibodies are injected (EMA).

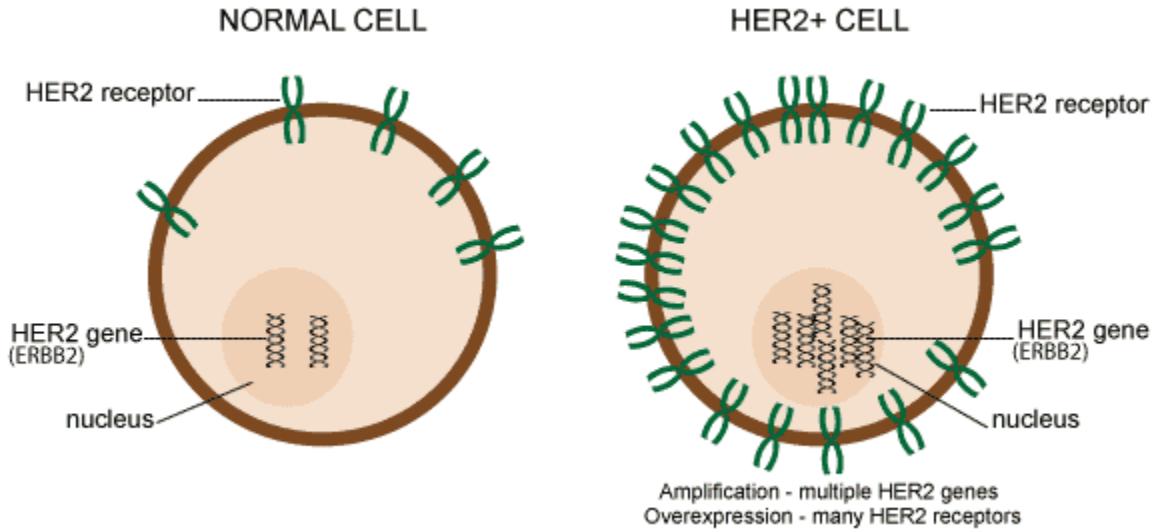

Figure 3. illustrating HER2 receptor in healthy and cancer cell [14].

Aim and Outline of the case study

Process design and regulatory challenges are two of the most important aspects of any pharmaceutical production line. Therefore, in order to investigate potential regulatory, quality, and process design of CM systems, a mockup system was set up. For this purpose, in this study, a mockup CM system has been developed for the production of Trastuzumab. The process was presented as a case study to several companies and Next Bioform to

discuss and study the potential challenges to produce Trastuzumab from API to the final product with CM.

Process design

Upstream

Upstream in the manufacturing of biological drugs using cell cultures can be defined as steps which would allow the manufacturer to grow cells and produce the API in these cells. Furthermore, when a mammalian cell is being used, a bioreactor would be the preferred environment, and when growing a microbial, a fermenter is used. During the process, manufacturers would control the key parameters which allow the desired cell to grow. The key parameters can be listed as pH, temperature, time, and oxygen. Moreover, before the start of the process, all the raw materials would be checked and inspected [16]. In this study, an *"Integrated Continuous Bio manufacturing (ICB)"* was used meaning all of the raw material would enter to an end-to-end process.

Downstream

After the upstream process, the cells which now contain the desired protein would be transferred to the downstream step. The downstream process contains several process steps to gain the desired quality of the API by purification. In this case study, a downstream process was used based on the doctoral thesis of Joaquin Gomis Fons titled "*Design and Control of Integrated Continuous Processes for the Purification of Biopharmaceutical*". This integrated downstream process involves integrated steps for reducing or removing impurities and unwanted material through several chromatography steps. After the drug substance exits the bioreactor it would enter the *"Alternating tangential flow filtration (ATF)"* system to remove particles and then enter a surge vessel. Moreover, before the chromatography step, the drug substance would be transferred to a virus inactivation step which would allow the manufacturer to stop viruses from contaminating the product and further increase the purity of the drug substance. Based on this, the drug substance would go through three chromatography steps such as *"Cation-exchange chromatography (CEX)"* which is a form of *"ion exchange chromatography (IEX)",* which is used to separate molecules based on their net surface charge. *Furthermore, an "Anion-exchange chromatography (AEX)"* which is also a process that separates substances based on their charges using an ion-exchange resin containing positively charged groups, and continuous 2-column periodic capture.

Compounding step

After the downstream steps the drug substance would be transferred to a sterile filtration system for bacterial removal. In this case study the intermediate product would be transferred to a vial filling machine after the downstream process. After filling the vials, they would be transferred to a continuous freeze dryer.

According to the FDA and *"European Medicines Agency (EMA)"* data, more than half of approved treatments are lyophilized products and thus using a freeze dryer as a key step in the process. Freeze dryer is a low-temperature drying process which allows the manufacturer to convert solution into solid powder form (FDA, EMA). Moreover, freeze dried powder is easy to store and fill in vials. Moreover, it could be dissolves prior to administration, usually via intravenous injection. For more than 50 years, batch freeze-drying has been performed which was proven as a reliable process. However, due to the uncontrolled nature of the process and uneven heat transfer among the vials, the industry has been investigating the option to replace traditional freeze dryer to a continuous freeze dryer [17]. In a continuous freeze dryer, the vial would go through a concept of vial rotating, where the cooling and freezing is achieved by using a flow of sterile gas [17] [18]. Furthermore, a condenser system continuously removes the condensed water. Continuous freezer dryer has several advantages over a normal batch freeze dryer including more control in overall process and more equal heat distribution. However, due to its complexity, and as an expensive technology, it has not been implemented yet in a meaningful number in the industry. Moreover, this step was added to increase the complexity of the case. Due to the reason that a lot of biopharmaceutical products do not need such steps and would be shipped to the consumers in liquid form.

Finally, after a continuous freeze dryer, the vials would be transferred to the capping machine. There, vials would be capped and shipped to the storage.

Critical Quality Attribute

Trastuzumab is a brownish-yellow colored powder which is shipped in 15-20 mL glass vials (EMA). The excipients used in this drug are L-histidine hydrochloride monohydrate L-histidine α, α-trehalose dihydrate polysorbate 20. One of the differences between batch and CM comes from the *"Critical Quality Attribute (CQA)"and "critical process parameters (CPPs)"*. These parameters are developed by the process engineers and

chemists which have developed the process and have a very good understanding of the process and its environment. CQA indicates if the batch can succeed and be accepted. Moreover, these CQA parameters have a direct impact on the product safety and patient life. The CQAs should be identical, irrespective of the way of production. However, the CPP would be changed depending on the mode of process. In batch systems, the manufacturer has complete control on the process CQA. In order to convert to CM, the manufacturer needs to present a strategy to authorities which indicates that the manufacturer has complete control strategy on the CQA and there are no differences when it comes to control strategy of CQA. Moreover, purity, molecular weight distribution, pH, concentration, osmolality, excipients, endotoxin levels are some of the examples of attributes that are impacted by downstream and are certain to affect the safety and efficacy of the biologic. As can be seen in table 2, some of the important CQA examples for production of Trastuzumab are mentioned [19].

Table 2. illustrating CQA example of the designed process.

CQA	Risks	Cause	Control points
Antibody binding	Efficacy	Formulation, storage	Bioreactor
Protein content	Efficacy	Manufacturing process	Bioreactor, Downstream
Appearance	Efficacy, Safety	Formulation, Manufacturing process	Bioreactor, Freeze-dryer
Product Stability	Efficacy, Safety	Manufacturing process	Freeze-dryer
pH	Efficacy	Formulation	Bioreactor
Particulate Matter	Safety/ Immunogenicity	Manufacturing process	Sterile Filtration, Freeze-dryer, Downstream, Bioreactor
Microbiological	Safety/ Immunogenicity	Formulation, Manufacturing process	Bioreactor, Downstream
Excipients	Safety/Efficacy	Formulation, Manufacturing process	Bioreactor, Downstream, Upstream
Endotoxin	Safety/Efficacy	Formulation	Bioreactor

Batch Definition

As could be found in the ICH guideline Q13 section 2 and Q7 which describes and gives guidelines to the manufacturer in order to define their batch in the CM system, the definition of the batch could be defined for all modes of CM [10]. It is also stated that the manufacturer can define the size of produced batch based on the following statements:

1. “Quantity of the input material.”
2. “Quantity of output material.”

3. “Run time as defined mass flow rate.”

In this case study, after observation and through investigation, it was decided to define the batch after the sterile filtration and when the intermediate product is transferred to storage space. This definition was reached as that after the sterile filtration and storage space it is the first breaking point in our process.

Results and Discussion

Initial Suggestion for the CM Process

Based on all the needed equipment and the purification steps taken to produce trastuzumab, a process was set up as illustrated in figure 4. Before entering the process, all the raw materials are tested and inspected in order to follow all GMP procedures. In the next step, the raw material would be transferred into a mixing tank. After mixing, the Product mixture is transferred to a bioreactor and after that it would follow a chain of downstream steps in order for the intermediate product to be purified as desired. These downstream steps include ATF filtration, columns filtration, and virus inactivation step. In the next step the purified API would be delivered to a second mixing tank where formulation is performed. This step would allow the manufacturer to add needed excipients to the process. Following the mixing tank, the intermediate product would enter a sterile filtration unit. In the next step, the intermediate product would be transferred to a filling machine and would be poured in the glass vial. All the vials would go through a continuous freeze-dryer and would be capped after the freeze drying process.

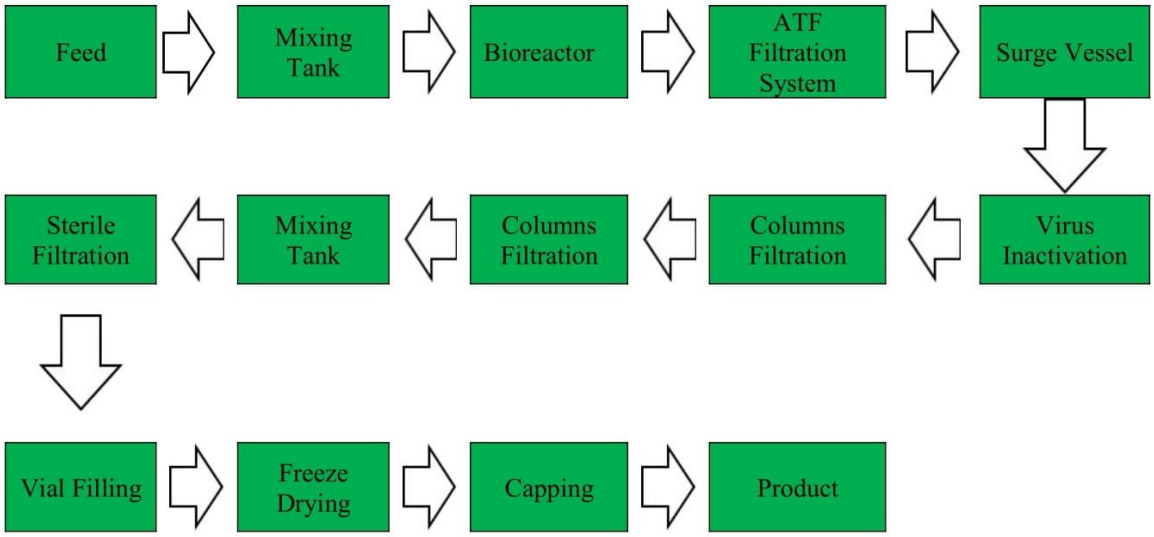

Figure 4. illustrating the initial process design.

Interviews

The initial process was presented to several companies and regulation professionals within the cooperation of Next BioForm. In these interviews, the main aim of the project and thesis was explained following by presenting the process in order to discuss the challenges and regulatory and technical issues. After having long discussions with the professionals from different companies, it has been decided to classify the obtained results in three categories including regulatory, quality and technical perspectives and economical aspects. All the questions are listed as can be found in appendix 1.

1. Regulation perspective

Converting the batch to CM system could be considered as a major change from what health agencies are used to seeing regarding documentation. Whenever there are major changes the expectation is that the manufacturer would have a very deep understanding of the process and every step impact on the overall process. Furthermore, when it comes to process and process quality, there are several criteria regarding protein therapeutics. Proteins are large molecules unlike small molecules and there are a lot of areas which are still being investigated like lack of complete control when it comes to protein characterization. As a result, if a manufacturer decided to conduct such major changes in

the production line of protein therapeutics, every aspect of each step and process should be investigated and it should be proven that the product is safe. Due to all these reasons, major changes in the pharmaceutical industry are not easy to be made. Moreover, due to the fact that there are not any "*standard operating procedure (SOP)*" for the manufacturer to follow in these cases and guidelines are considered only as guide and are not mandatory. Thus, the biggest risks when it comes to regulation would be unknown and uncertainties during the process.

A noticeable comment was made during the interview stating that with small molecules, manufacturers have the second regulatory opportunity to rework the batch incase of impurities. For small molecules and small peptides, several analytical methods are available that could control and characterize the material. Should the drug substance not be within set specification limits, reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps that are part of the established manufacturing process is generally considered acceptable. Therefore, manufacturers are forced to wait for the result of analysis as they have the option to redo the process which could save them resources. However, with biomolecules it is not possible to do a rework. Thus, because of the nature of the process, if there is any problem, you need to throw the batch away so it could be possible to sample and wait for the results later. Due to this reason, not all changes in the structure of biological material can be analytically detected. Moreover, based on the regulatory experiences, the amount of testing decreases when the manufacturer goes from laboratory to commercial scale. Thus, the manufacturer needs to provide for the authority's process specification and control stages.

One of the advantages which could be mentioned is "scaling out". In order to increase the production rate there are several options including scaling up, and scaling out. Scale up would require intensive regulatory hurdles in order to show if the process would have the same characteristics. However, one of the advantages of having a CM system is scaling out, which allow manufacturers to add more discrete units of operation to their production line. Scaling out would allow manufacturers to have several production lines at the same time running as such increasing the production rate.

In order to store produced intermediate product in the event of malfunction, holding spaces should also be considered. Thus, the equipment malfunction should be part of the risk assessment of the process. Additionally, to address the drug substance storage problem during equipment malfunction, there should be an investigation to figure if the material could be stored and also find the proper environment needed. In the case of malfunction,

the manufacturer is allowed to mix API together at holding time if the manufacturer could provide analysis results that illustrate the API is within the specifications as described in ICH Q7. Thus, manufacturers are not allowed to dilute impurities meaning that it is not acceptable to mix a batch within specification with a batch which is out of specification. Also, it should be clear that this is only valid for API, drug products cannot be mixed at any stage.

In conclusion, from the two interviews which were conducted around the regulatory aspect of the case the following information was conducted:

1. Although continuous freeze drying could be considered as a complex technical step, based on the regulatory perspective it is considered as a step without too many regulatory hurdles.
2. The most difficult issue of the CM process from a regulatory point of view was defining the batch.
3. How to control the process impurities and how to control them during upstream and downstream steps. In order to overcome these regulatory hurdles, the manufacturer should illustrate the control strategy in their production line and the action needed when impurities were detected.

2. Quality and Technical Perspective

In general, one advantage of CM regardless of unit of operation is to offer a high throughput, meaning that the manufacturers have high volume and high product demands. Due to this reason, CM would have advantages over batch systems. An example of this situation could be seen in the Covid pandemic of 2020 where the whole global capacity of the pharmaceutical industry was not capable of providing the market demand. As observed during the pandemic, most of the vaccines were shipped in the frozen state, not freeze dried. However, freeze drying would have provided advantages over frozen due to complexity of storing the vaccines in -80°C degree. Furthermore, there are several challenges in shipping and distributing the vaccine in the frozen environment. However, the reason why companies decide to proceed such is the concept of capacity. CM systems have the edge over batch systems when it comes to high volume high demand products.

The need to have a holding point has been brought up. The reason to have a holding point between steps was determined as to have space in the event of malfunction and tests. Moreover, based on the companies experiences with which this interview was conducted,

holding points play a key part to store the intermediate product till the result of quality control is determined, sterile filtration for instance. One of the tests which is required is testing the filter to see if they are working properly. Furthermore, it was noted that depending on the manufacturer quality control department capacity, it is likely that some of the analyses and tests need to be sent to an external laboratory. There might be several days or weeks to get the results back. Thus, in order to catch up, manufacturers need a holding space and storage unit to store the drug substances. As has been discussed and presented, one of the concerns was the complexity of continuous freeze dryers. Due to innovation and complexity of the continuous freeze dryer, new protocols for maintenance, internal standard operating procedures for cleaning are needed. Additionally, installing a CM system would be beneficial in the designed process due to the freeze dryer step which is determined as a bottleneck. In other words, the freeze drying step is the limiting step. Owing to this reason, putting a continuous freeze dryer would accelerate the production rate compared to a normal batch system.

Reviewing the proposed case, it was understood that implementing and installing such a CM process is feasible. On the other hand, the continuous freeze dryer is a new concept that has not been implemented yet and has not been known among experts. Due to this reason there might be some technical challenges for any companies who wants to implement them in their process.

In general, it could be concluded that when it comes to in-process control, continuous freeze dryer is heterogeneity and shows more control on the process. However, the question which arises from this process control would be how to define the batch and what kind of in control process could be deployed. A topic which was brought up during one of the interviews was the sustainability aspect of the CM process compared to the batch system when it comes to energy consumption. Based on the experience conducted from the industry in the past 20 years and the new UN guideline on sustainability, if a manufacturer could illustrate that CM is going significantly greener compared to the batch system and the process would have a smaller carbon footprint, it is easier to convince the manufacturer to invest on upgrading their batch systems into CM systems.

3. Economical Aspect

In order to have a better understanding of the economical aspect to switch from batch to CM, an interview was conducted with a corporate strategy consultant. Based on the

information which was provided in the presentation, the following result was obtained. Owing to the complexity of the pharmaceutical industry and high levels of competitiveness, a successful solution should meet a balance between supply, demand, and products. Due to the increasing number of patients diagnosed with breast cancer in the past 40 years (WHO), the use of anti-cancer treatment has grown. Based on the market analysis of Trastuzumab, the demand is increasing and by the year 2025 the market value is expected to increase to $4.25 billion [20]. Demand is one of the important factors considering the fact that in the year 2020 more than 2.3 million women were diagnosed with breast cancer (based on WHO database) leading to the necessity of having access to an effective treatment. Supply is the other vital factor, based on the current global supply chain problems which is the result of the new geopolitical problem, a lot of companies are facing supply shortages. For a pharmaceutical company to be able to meet the demand and the flow of the production line, they need to invest in new ways to meet new challenges. A CM system would be an ideal answer to meet the demand and production of the product. Some of the challenges many manufacturing companies are currently facing can be listed as below.

1. The heavy flow in the production line due to high demand.
2. Recalibrating the production line requires meeting compliance.
3. Maintenance and introducing new technology to the existing production line.

Reviewing the proposed case, the following opportunities and challenges were determined. As has been discussed and presented, one of the concerns was the relative production rate between a CM and a batch system. In order to investigate the validity of investments so as to convert a batch to a CM system, it is desired to determine the demand for the treatment in the long run. Furthermore, there should be an assessment of the demand and priority of the drug in the present timeline. This assessment is necessary to justify the investment needed. It should be noted that there should be a demand that is higher than the supply for the produced drug so converting to the CM system could be justified. One of the most challenging aspects of the CM system is the intense capital investment. In order to have a successful business plan, there should be an option to return the initial investment in a 2-5-year period.

Based on the interview conducted, installing a CM system requires having a variety of production lines so that the CM system could help manufacturers to adjust itself with supply and market demand. CM systems could be useful due to their flexibility which would allow the manufacturer to have faster response to changes in the market and varying market demand. Furthermore, due to the nature of the pharmaceutical industry, which

involves a lot of research and clinical trials, this flexibility is needed in order for the manufacturers to adjust themselves with the market. Competition in this industry is another factor required to be considered since new drugs with less side effects are introduced to market continuously introduced to the market. A flexible production line is required for the manufacturer to be able to compete in the market and change their production line as fast as possible.

Final Design

After all the interviews and discussing the case with professionals both from a regulatory and a quality control point of view, it was decided to implement following changes to the process design as can be seen in figure 5.

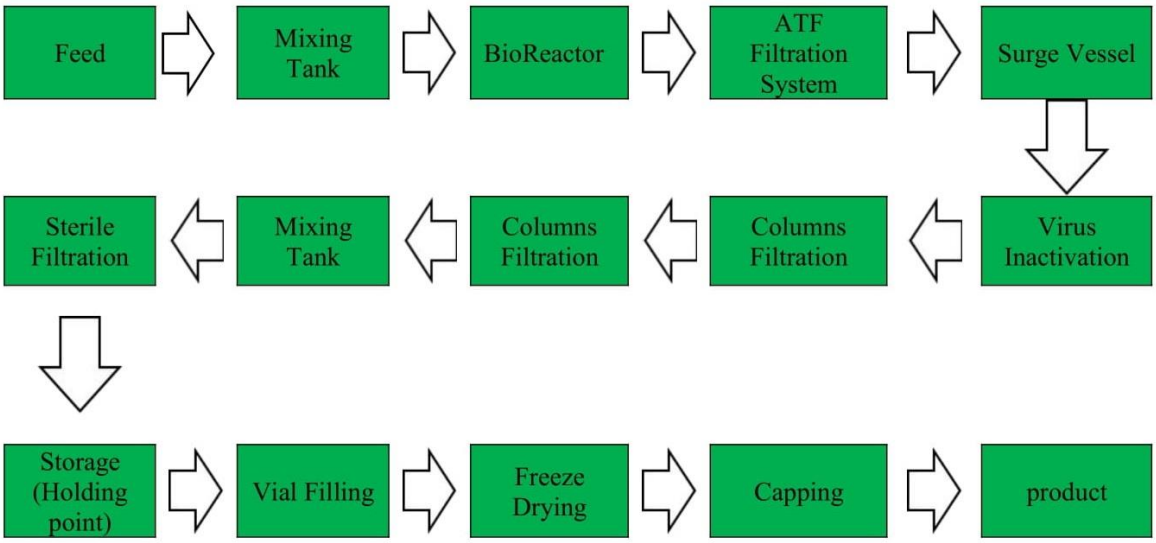

Figure 5. illustrating the final process design.

The need for holding time was brought up in almost all the interviews and based on the information which was gathered, it was decided to place a holding point after the filtration step and when the downstream part is finished. Additionally, continuous freeze dryer was identified as the most important part of the process. Although from a regulatory point of view continuous freeze dryer is not considered as a big regulatory hurdle. On the other hand, there are several challenges which need to be considered including lack of technical support and complexity.

It was decided to have two alternating sterile filtration lines, one used in the process, the other one being cleaned and going through demanded filtration analysis to ensure its integrity, should be used. Holding points were placed after the sterile filtration, which in this stage would allow the manufacturer to check the next step in the process for any malfunction. Moreover, it would give the manufacturer the time needed to perform tests on the intermediate product which in this stage would be considered as a batch for test including any impurities, proper work of filtration, mutation, pH and molecular weight. Furthermore, some of these tests could be implemented in the process as an on-line control system during the process.

During one of the interviews one of the companies mentioned the lack of infrastructure to perform their test and outsourcing it to a third party laboratory. In such a situation several storage tanks and holding points during the process are needed. These holding points would allow the process to continue at the same time storing several batches till the result data would be ready. Such action could be acceptable due to the reason that at this point of the operation stage all the critical points and areas have been defined and counter action has been developed which would allow the manufacturer to have an end-to-end process.

It was concluded that due to the hurdle to convert the existing production lines to CM it would make more sense to implement these new systems for the upcoming and future products. This decision is made due to the reason that it would be harder for manufacturers to convince the authority for the conversion of their production line to CM compared to starting a new production line with CM systems. Furthermore, although technology would allow the manufacturer to convert their systems to CM, from an economical point of view it is still difficult to convince the company to invest in CM. Due to reasons like lack of studies and investigation in the power consumption, sustainability, and investment return. These are significant reasons which could affect the company strategy to invest in converting an existing production line into CM.

Conclusions

The aim of this thesis in the beginning was to study the regulatory aspect of the CM system, because at the starting stage of this thesis it was believed that the biggest problem to implement CM systems is regulatory point of view. However, it was understood from the interview with professionals, that there are several other setbacks like technical and economical hurdles. Overall it can be said that implementing CM or transforming or rebuilding an already existing production plant into a CM-process production side is not economically and financially sustainable. Especially the capital intensitivity and regulatory risks from a legal perspective makes transforming production lines into CM plants uneconomical. On the other hand, it can be stated that companies or research facilities, which are in need for higher production capacity and therefore are willing to build new production lines and plants, benefit highly from relying on a CM system.

Future work

Continuous Manufacturing is not a new concept and it has already been implemented to some degree into the pharmaceutical industry. However, there is still not a strong argument to convince the industry to invest to convert their batch system into CM. In the future it would be interesting to study and investigate a comparison between CM and batch systems when it comes to power consumption. Additionally, it would be necessary to conduct the sustainability of CM and compare them to batch systems. These areas need to be studied in order to help the industry to have better understanding of the benefits of CM and their implementation into the industry.

References

[1] Hock, S. C., Siang, T. K., & Wah, C. L. (2021). Continuous manufacturing versus batch manufacturing: benefits, opportunities and challenges for manufacturers and regulators. Generics and Biosimilars Initiative Journal, 10(1), 1-14.

[2] Annual Report Electronic Arts 2022 | Statista. Statista. 2022 . Available from: https://www.statista.com/study/112957/annual-report-electronic-arts-2022/.

[3] Domokos, A., Nagy, B., Szilágyi, B., Marosi, G., & Nagy, Z. K. (2021). Integrated continuous pharmaceutical technologies—A review. Organic Process Research & Development, 25(4), 721-739.

[4] Müller, D., Klein, L., Lemke, J., Schulze, M., Kruse, T., Saballus, M., ... & Zijlstra, G. (2022). Process intensification in the biopharma industry: Improving efficiency of protein manufacturing processes from development to production scale using synergistic approaches. Chemical Engineering and Processing-Process Intensification, 171, 108727.
Wahlich, J. (2021). Review: Continuous Manufacturing of Small Molecule Solid Oral Dosage Forms. Pharmaceutics 2021, 13, 1311.

[5] Lee, S. L., O'Connor, T. F., Yang, X., Cruz, C. N., Chatterjee, S., Madurawe, R. D., ... & Woodcock, J. (2015). Modernizing pharmaceutical manufacturing: from batch to continuous production. Journal of Pharmaceutical Innovation, 10(3), 191-199.

[6] Wahlich, J. (2021). Review: Continuous Manufacturing of Small Molecule Solid Oral Dosage Forms. Pharmaceutics 2021, 13, 1311.

[7] Badman, C., Cooney, C. L., Florence, A., Konstantinov, K., Krumme, M., Mascia, S., ... & Trout, B. L. (2019). Why we need continuous pharmaceutical manufacturing and how to make it happen. Journal of pharmaceutical sciences, 108(11), 3521-3523.

[8] FDA leads global work on continuous manufacturing approaches to up quality, supply chain resilience - Long-Awaited ICH Q13 draft guidelines on CM of drug products released | JD Supra. JD Supra. (2022). Retrieved 1 June 2022, from https://www.jdsupra.com/legalnews/fda-leads-global-work-on-continuous-3803791/#:~:text=There%20are%2010%20approved%20continuous,from%20batch%20manufacturing%20to%20C.

[9] Allison, G., Cain, Y. T., Cooney, C., Garcia, T., Bizjak, T. G., Holte, O., ... & Zezza, D. (2015). Regulatory and quality considerations for continuous manufacturing. May 20–21, 2014 continuous manufacturing symposium. Journal of pharmaceutical sciences, 104(3), 803-812.

[10] ICH guideline Q13 on continuous manufacturing of drug substances and drug products.

[11] Müller, D., Klein, L., Lemke, J., Schulze, M., Kruse, T., Saballus, M., ... & Zijlstra, G. (2022). Process intensification in the biopharma industry: Improving efficiency of protein manufacturing processes from development to production scale using synergistic approaches. Chemical Engineering and Processing-Process Intensification, 171, 108727.

[12] Domokos, A., Nagy, B., Szilágyi, B., Marosi, G., & Nagy, Z. K. (2021). Integrated continuous pharmaceutical technologies—A review. Organic Process Research & Development, 25(4), 721-739.

[13] Overview of comments received on ICH Q13 Continuous Manufacturing of Drug Substances and Drug Products (EMA/CHMP/ICH/427817/2021)

[14] Herceptin® (trastuzumab) for HER2+ Cancer. herceptin. (2022)., from https://www.herceptin.com/hcp/treating-HER2-cancer.html.

[15] HER2 Receptor and Hormone Receptors ER+ Influence On Breast Cancer. Whathealth.com. (2022). From https://www.whathealth.com/breastcancer/her2receptor.html.

[16] Biomanufacturing Technician - Upstream. Biotech-careers.org. (2022). Retrieved 1 June 2022, from https://www.biotech-careers.org/job/biomanufacturing-technician-upstream.

[17] Corver, J., Van Bockstal, P. and De Beer, T., 2022. A continuous and controlled pharmaceutical freeze-drying technology for unit doses. [online] European Pharmaceutical Review. Available at: <https://www.europeanpharmaceuticalreview.com/article/70823/continuous-controlled-pharmaceutical-freeze-drying-technology-unit-doses/>

[18] Adali, M. B., Barresi, A. A., Boccardo, G., & Pisano, R. (2020). Spray freeze-drying as a solution to continuous manufacturing of pharmaceutical products in bulk. Processes, 8(6), 709.

[19] FDA, Product quality review for the application 761081Orig1s000.

[20] WIRE, B. (2022). Global Trastuzumab Biosimilars Market Research Report 2021: Analysis & Forecasts 2015-2020, 2020-2025F, 2030F - ResearchAndMarkets.com. Businesswire.com.,

from https://www.businesswire.com/news/home/20211210005264/en/Global-Trastuzumab-Biosimilars-Market-Research-Report-2021-Analysis-Forecasts-2015-2020-2020-2025F-2030F---ResearchAndMarkets.com.

Appendix

Case study questionnaire

After a presentation on the case and the process, following question were asked:

1. Based on your experience have you seen any company implementing continuous Freeze dryers in their production lines.
2. Are there any difficulties in implementing continuous freeze dryers from a quality and regulatory perspective?
3. Based on the presented process, where is the best place to examine the product and have control points?
4. Based on your experience, Is it better to have a hybrid CM instead of all the way continues?
5. Based on the previous interview the need to have a holding point was brought up. Where in the process would you believe that a holding point is needed.
6. Have you thought about the time needed to conduct the analysis?
7. Could process control be more robust for the CM system?
8. Which regulatory hurdles could a manufacturer face when converting from batch to CM?
9. How easy is it to link an end to end system for production of biopharmaceuticals? Do you need to have a breaking point?
10. What action is needed in the event of equipment malfunction?