Universidade de Lisboa

Faculdade de Farmácia

Continuous versus batch manufacturing of oral dosage forms. Analysis of current worldwide implementation

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Monografia orientada pelo Professor Doutor Luís Filipe Gouveia,
Professor Auxiliar.

Mestrado Integrado em Ciências Farmacêuticas

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

Tradicionalmente, o fabrico de formas farmacêuticas orais é feito pela produção de lotes, mas nos últimos anos a indústria farmacêutica tem vindo a ser pressionada para melhorar a eficiência e qualidade de fabrico. Com o aumento da exigência por parte das autoridades reguladoras e a diminuição das margens de lucro fez com que as indústrias farmacêuticas explorassem novas tecnologias de fabrico A produção em continuo tem sido considerada uma opção alternativa à produção por lotes para muitos fabricantes, visto que, geralmente produz produtos farmacêuticos de melhor qualidade e de maior rendimento, com tempo e custos reduzidos.

Apesar dos avanços consideráveis e do incentivo por parte das autoridades reguladoras (FDA, EMA) através da emissão de diretrizes adequadas, a utilização da produção em continuo na área farmacêutica ainda é limitada devido a uma série de desafios relativos ao desenvolvimento de processo e à garantia de qualidade que têm impedido os fabricantes de adotar esta tecnologia.

Esta dissertação aborda as principais alterações relacionadas com a implementação da produção em continuo relativamente à produção por lotes e avalia o tipo de produção (produção em continuo vs produção por lotes) mais rentável tendo em conta vários fatores. São ainda apresentados e discutidos exemplos de empresas que já utilizam a produção em continuo, bem como alguns medicamentos fabricados com esta tecnologia.

Palavras-chave: Produção em continuo; Produção por lotes; Análise Custo-eficácia; Indústria Farmacêutica.

Abstract

Traditionally, the manufacture of oral pharmaceutical forms is performed by batch manufacturing, but in recent years the pharmaceutical industry has come under pressure to improve manufacturing efficiency and quality. With increasing requirements from regulatory authorities and decreasing profit margins, pharmaceutical companies have been exploring new manufacturing technologies. Continuous manufacturing has been considered an alternative option to batch manufacturing for many manufacturers, as it generally produces better quality and higher yielding pharmaceutical products, with reduced time and costs.

Despite considerable advances and encouragement from regulatory authorities (FDA, EMA) through the issuance of appropriate guidelines, the use of continuous manufacturing in pharmaceuticals is still limited due to a number of process development and quality assurance challenges that have prevented manufacturers from adopting this technology.

This thesis is focused on the main changes related to the implementation of continuous manufacturing relative to batch manufacturing and the evaluation of the most cost-effective type of production. Examples of companies already using continuous manufacturing, as well as some drugs manufactured by using this technology will be presented and discussed.

Keywords: Continuous manufacturing; Batch manufacturing; Cost-effective analysis; Pharmaceutical Industry.

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Abbreviations

BM: Batch Manufacturing

CM: Continuous Manufacturing

DoE: Design of Experiments

EMA: European Medicines Agency

FDA: Food and Drug Administration

GMP: Good Manufacturing Practices

ICH: Harmonization of Technical Requirements for Pharmaceuticals for Human Use

PAT: Process Analytical Technology

PMDA: Pharmaceuticals and Medical Devices Agency

QbD: Quality by Design

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1 Introduction

The Pharmaceutical industry is facing the largest ideological revolution since the industrial drug manufacturing. (1) Traditionally, drug products are manufactured in batch mode, however, continuous manufacturing (CM) has been gaining serious interest as it is necessary to decrease costs, improve process efficiency, achieve optimal use of equipment and flexibility in production capacity, due to the competition between manufacturers and the increasing demand of low-cost drugs. (1–5) In recent years, improvements in science and engineering have been developed that have facilitated the implementation of CM. Pharmaceutical regulatory authorities encourage pharmaceutical industries to apply CM because they recognize its benefits over the traditional batch configuration, in terms of cost-reduction, improved efficiency, ease of automation, better controlled processing, reduced energy, reduced waste, less footprint, ease of scale up, less material handling, and consistent product quality. (6,7)

In Batch manufacturing (BM), usually the materials from a particular stage are tested off-line and stored in a separate location before being sent on to the next stage. If the in-process material fails to meet the quality standards, it may be rejected or, in some cases, reprocessed before continuing on to the next process stage. (6) In continuous manufacturing, each material produced during the process is sent directly and continuously to the next production step. In each production step it is necessary to produce an intermediate material or product with acceptable specifications. Thus, CM, often involves a higher level of process design relative to BM to ensure adequate process control and product quality.(1,6) Companies are willing to change from batch to continuous processes if there are immediate benefits, such as economic returns, high speed of development and process safety to reach the required product quality.(8)

The present review aims to present the main changes related to the implementation of continuous manufacturing in pharmaceutical industry and to discuss the most economically advantageous production. Besides, some examples of companies using continuous manufacturing and respective commercialized products are presented.

1.1 Manufacture of solid products

Currently, most medicinal products are orally administered in solid form, as tablets or capsules. These contain two groups of materials, active substances and excipients. The active substance is designated as any substance or mixture of substances intended to use in the manufacture of a medicinal product, which exerts a pharmacological, immunological or metabolic action, in order to restore, correct or modify physiological functions or to establish a medical diagnosis. The active substance is then combined with excipients (inert components) to facilitate the manipulation, manufacture, administration and dissolution of the product. (9–11)

There are several types of production of oral pharmaceutical forms, being batch manufacturing the most widely used. This type of production has been used for more than half a century and is likely to continue for a long time. Batch manufacturing is based on a sequence of individualized start and stop manufacturing steps, such as weighing, mixing, granulation, drying, compression, and coating. At each stop of a manufacturing step, quality control analysis or quality inspection is usually required. The need to stop, wait for results and restart the process can be extremely time consuming, creates downtime for manufacturing equipment, and can also create undesirable quality attributes of the intermediate products such as powder segregation. This costs the industry approximately $50 billion dollars per year. Despite the associated disadvantages, batch production is still often used because of its low set-up costs (Table 1). It is also great for the manufacture of small quantities of pharmaceutical products, in which their composition or formula requires the production of a batch. While batch production is common due to these benefits, continuous manufacturing has entered as a prospective alternative to reduce inefficiencies and higher quality using modern technology (Table 1).(8)

Continuous manufacturing is a highly automated process that allows the production of a product with minimal intervention and process downtime. Throughout the process it is important to measure in real-time the optimal endpoint of a specific step before going on to the next one. To achieve this, state-of-the-art technology such as Delta V, PAT, and spectroscopic measurement of content uniformity are used to control critical process parameters, as to measure critical quality attributes. Although the investment amount is higher when compared to batch manufacturing, the reduction in operating

costs is expected to improve the company's efficiency (**Error! Reference source not found.**).

Table 1. Features of batch and continuous manufacturing. (12)

	Batch Manufacturing	**Continuous Manufacturing**
Raw material input/ Product output	Raw materials are injected into the process operation non-continuously, and the product is discharged collectively after the operation is completed.	Raw materials are injected into the process operation continuously, and the product (product material) is discharged continuously and sequentially after a certain time.
Production processes	Each operation is started and stopped repeatedly by operator handling.	Production is continuous through interconnected unit operations and automation without operator management.
Production facility area	Large space needed	Space saving
Scaling-up	Individual verification processes and dedicated equipment are needed for each scale at the development and validation, and different equipment is needed for commercial production.	Equipment required for development can be designed in the actual production, and a quick transition to commercial production is possible by simply adjusting the production time.

1.2 Definition of Batch and Continuous Manufacturing

Batch and continuous processes can be defined in different ways:

- Batch manufacturing: The product is processed via a series of sequential unit operations (e.g., blending, granulation, drying, tableting, coating, and packaging) to manufacture the final dosage form. Each unit operation is run using specific settings (defined during method development and validation) to modulate the properties of the material and when the predetermined endpoint (often as a function of time) of a specific unit operation is reached, the process cycle is stopped and the intermediate materials are packed off and stored in warehouses. Once the quality of the intermediates has been assessed in control labs using a wide array of off-line (and often destructive) analytical tools, the material is reloaded into the process to perform the next unit operation. As off-line quality analysis can take hours, days or even weeks, the material throughput time of a batch manufacturing process is significantly delayed using this segmented manufacturing approach. If the predefined quality standards after a unit operation are not met, the entire batch is either rejected or reprocessed, resulting in significant economic loss. (6,13)
- Continuous manufacturing: The material is continuously charged and discharged from the process, respectively, throughout the time of the process. (6,13) Quality assurance during a continuous process requires continuous monitoring of critical process parameters, as well as continuous inspection of quality attributes of raw materials, intermediates and end product via at-line, on-line or in-line measurements in the process stream. Deviations can be rapidly detected and real-time adjustment of process parameters becomes possible via feedback loops to keep the system within its operational range and minimize material loss. Handling of intermediates in a continuous process is not required as raw materials are directly converted into finished products via an integrated process chain, thus reducing material throughput time. (11)

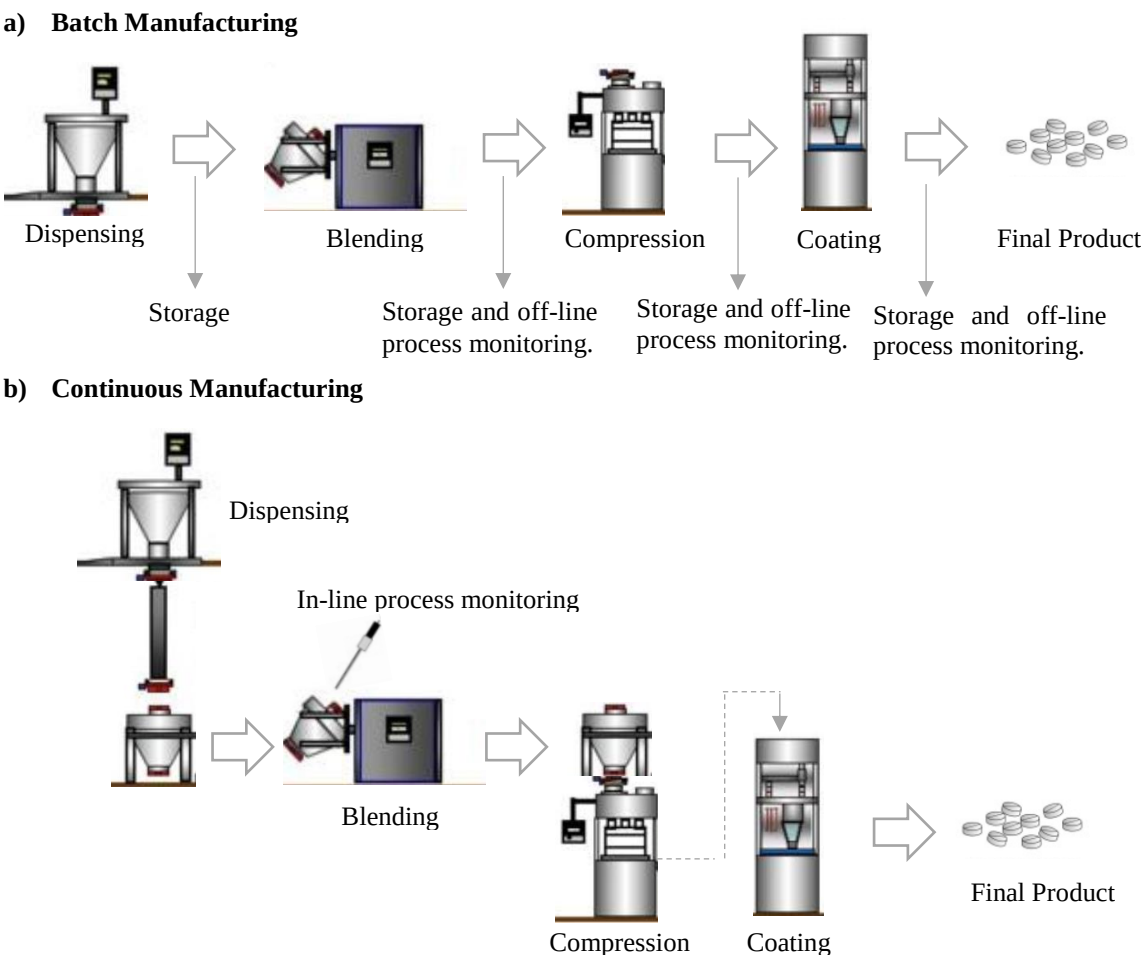

Figure 1 Representation of batch and continuous manufacturing processes of drug product. a) The raw materials and the product are loaded and discharged, respectively along the process and over time. Between stages, the intermediate product is tested and storage. b) The raw materials are loaded at the initial time and the product discharged at the end of the process. The product is tested throughout the process.

1.3 Batch versus continuous manufacturing of dosage forms

In recent years, the growing demands from the drug market, drug shortage problems, the desire for reduced processing costs, higher requirements for consistent quality and, most importantly, the need for higher productivity placed into the manufacturers have stimulated pharmaceutical companies to investigate the opportunities of continuous manufacturing. In fact, manufacturers are under constant pressure to minimize the drug development time while maximizing the total output. As batch manufacturing has wasteful at different levels, transition to continuous can result in significant gains. (6,8,11,14) The table below summarizes the advantages and disadvantages of batch and continuous manufacturing.

Table 2 Pros and cons of Batch and Continuous Manufacturing

	Advantages	**Disadvantages**
Batch Manufacturing	Well-established processes with regulatory approval Low investment	High Costs Time-consuming process Variability between process Prone to human Error
Continuous Manufacturing	Agility Costs' reduction Robustness Real-time Quality Assurance Best Engineering System Decreased cycle time Reduced floor space Flexibility	High initial investment Loss of manual jobs New safety considerations required Requires highly trained personnel New processes need to be validated and regulatory approved Limited possibilities to reconfigure the unit operations

Although the batch manufacturing has been the most used, this is considered a very costly and time-consuming process as it involves frequent stopping, cleaning, and restarting of the manufacturing lines, which leads to high energy consumption, intensive labor and material loss. In addition, the quality assurance of the batch manufacturing is demanding. Materials are only transferred from one unit to another in quarantine, where testing of the materials must be performed before their release to the next step. Nonconforming materials are discarded or reprocessed in certain cases. However, shipping and storing intermediate products between batch manufacturing operations elevate the cost and increase the potential of deterioration, contamination, and error. Also, batch-to-batch variability that arises from the high impact of the human element is a great challenge in batch manufacturing. Therefore, this system is also susceptible to more failures that might result in drug shortage in the market, particularly if a product fails in the final stages of production.(8,14) The current manufacturing process followed by most of the pharmaceutical manufacturers has limitations in terms of flexibility as unit operations are performed in different locations and process controls are not dynamic. (15)

Continuous pharmaceutical manufacturing enables important improvements to society, patients, manufacturers, and pharmaceutical companies.(13) CM has a great potential to address issues of agility, flexibility, costs, and robustness in the development of pharmaceutical manufacturing processes. (16,17) The transition from batch manufacturing to continuous manufacturing requires an initial investment in order to upgrade manufacturing equipment and install appropriate process analytical tools to control the process and develop control strategies which allow to ensure equivalency of the two processes. (15) Flexibility is a major advantage of continuous manufacturing: new processes can be developed rapidly using the existing continuous manufacturing lines. In this type of production, the attributes of the process (e.g., drying time, content uniformity, weight) can be controlled/adapted in real-time and the system parameters (e.g., RH, temperature) can be measured. The CM facilities require less space since the equipment is in one room. It is estimated that there is a reduction of about 80% in the space taken up by intermediate product storage when compared to batch production. (13)

1.4 Regulatory Environment of continuous manufacturing

Regulatory agencies, including the Food and Drug Administration (FDA), European Medicines Agency (EMA) and Pharmaceuticals and Medical Devices Agency (PMDA), advocate continuous manufacturing as a way of modernizing the pharmaceutical industry and have encouraged industries to adopt this type of manufacturing.(6,13,18) They believe that CM has the potential to provide an higher level of product quality assurance, providing the maximum flexibility and agility for pharmaceutical manufacturers, and it is strongly aligned with Quality by Design (QbD) for pharmaceutical development. There are no major regulatory hurdles for manufacturers implement continuous manufacturing, as there is a general agreement that continuous manufacturing can be successfully implemented executed within the current regulatory framework.(3,5,6,13)

To encourage the transformation from batch manufacturing to continuous manufacturing, regulatory agencies (FDA, EMA and PMDA) established expert teams serving as primary points of contact for manufacturers: (19–21)

- FDA Emerging Technology Team;
- EMA PAT Team;
- PMDA Innovative Manufacturing Technology Working Group.

Several initiatives have also been developed for industries to invest in this type of production.(6,13) In 2003, appeared the first initiative “Pharmaceutical CGMPs for the 21s century- a risk based approach” and was followed by others, such as PAT Guidance 2004. The ICH has supported CM indirectly, for example, via ICH Q8 and Q9 in 2006, ICH Q8 R1 in 2009, and ICH Q11 in 2013. In 2019, FDA issued a new draft guidance entitled “Quality Considerations for Continuous Manufacturing”, covering several essential topics about CM, as important definitions of process dynamics and batches, control strategies and process validation. (8,19,20)

In 2021, the agencies further agreed to work in new ICH Q13 “Continuous Manufacturing for Drug Substances and Drug Products” and ICH Q14 “Analytical Procedure Development and Revision of Q2 (R1) Analytical Validation” , to establish the guidance on definitions, control, validation and regulatory requirements and the use of modern analytical technologies like Near Infrared (NIR) and Raman spectroscopy, as well as concepts like Real Time Release Testing and Quality by Design. (22)

2 Materials and Methods

This report consists of a bibliographic review, in which different online databases and indexing services such as Google Scholar, Pubmed, NCBI, b-on, Science Direct, Elsevier, SpringerLink were used.

Articles and publications with scientific arbitration were selected, published between 2005 and 2020. The terms used in this search were mainly: “continuous manufacturing”, “batch manufacturing”, “economic analysis”, “regulation and implementation worldwide”. These keywords were searched in both Portuguese and English language.

3 Results and Discussion

3.1 Challenges for continuous manufacturing implementation

With an increasingly competitive market, pharmaceutical companies need to lower the production costs of their drugs, so that they can offer the same quality at a reduced price. Thus, cost reduction in product development and manufacturing has become a major focus of innovation. In the last few years, pharmaceutical industries have been modernizing production, through the purchase of new (more efficient) equipment and some of them have invested in continuous manufacturing.

For those industries that decide to invest in continuous manufacturing, there are several considerations that must be considered. In Figure 2 the main changes for the implementation of continuous manufacturing are showed.

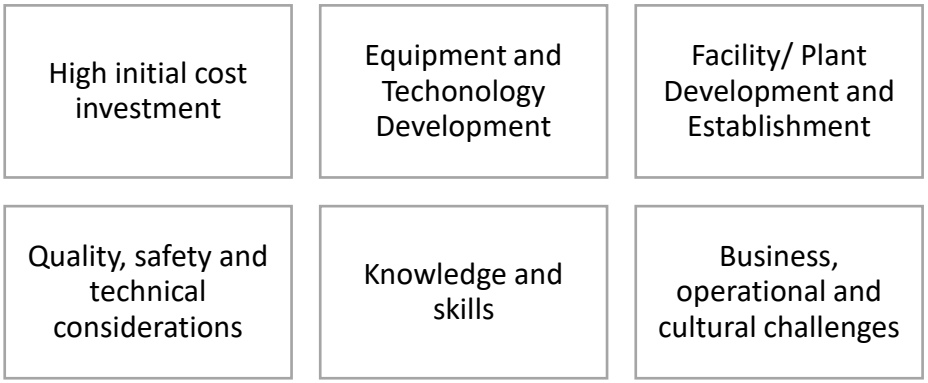

Figure 2 Main Changes for the implementation of continuous manufacturing

3.1.1 High Initial cost investment

The development of continuous manufacturing processes is costly, as it requires the use of automation and PAT software. Investment in continuous manufacturing is not a priority for most manufacturers as the initial cost is high and there is a need to justify the purchase of new equipment when the equipment used in batch production is still functional.(4,23) For generic manufacturers, initial investment is considered a significant hurdle as they operate on low profit margins and unpredictable demand for generic drugs would prevent them from investing in continuous manufacturing. (15)

A study carried out at Novartis GT showed that the investment required for the construction of a continuous manufacturing plant is lower when compared with the

investment required for batch manufacturing (approximately 310 vs 520 million euros) (24) For the construction of a continuous manufacturing plant for the production of Vertex, the investment exceeded 30 million dollars. (25) However the price of construction varies depending on capacity, technology, location, etc., thus, a pharmaceutical industry wishing to invest in the construction of a new site should take these costs into account and opt for the most cost-effective type of production.

Although the initial investment to implement continuous manufacturing is high, it is expected that, in situations of high production, the volume of the initial investment will be recovered in a short period of time.(15) Several studies have shown that continuous manufacturing can reduce production costs compared to batch manufacturing. A study carried out by the Novartis-MIT Center showed a significant reduction in labor costs and energy consumption, resulting in significant cost savings.(24) Thus, continuous manufacturing is an opportunity for industries to make long-term gains.

3.1.2 Equipment and technology development

To implement continuous manufacturing in a company, equipment intercommunication is necessary, as during the change of the production phase it is essential to transfer a product from one equipment to another. For this, industries must acquire equipment that allows this communication. In certain situations, it is possible to adopt the equipment already used in batch manufacturing, i.e., many of the equipment recently used in batch manufacturing already allow the change to continuous production with few alterations and a small investment to connect equipment among themselves. Besides the interconnection of equipment, it is necessary that they have state-of-the-art technology that enables real-time in-process control, allowing any deviation to be dealt with on time. PAT is fundamental in continuous manufacturing, since monitoring and control are the basis for production success. (26) Therefore it is necessary to validate methods that allow real-time process control. This validation must be carried out for each of the products that are to be transferred to continuous manufacturing and is based on the DoE. A predictive model with simulation capability must be built to define action limits, as well as a strategy to manage any process deviation by adjusting parameters. Control strategies should be devised to give constant assurance of process performance and quality. (18,27)

Thus, continuous manufacturing can be successful due to the combination of advanced technologies, improved equipment, precise controls, automation, and software.

3.1.3 Facility/ Plant Development and Establishment

Installing a continuous manufacturing line requires less space than batch manufacturing. Studies show that continuous manufacturing facilities require only about a third of the space when compared to the space required by batch manufacturing.(24)

Table 3 shows a case study carried out at Novartis AG, which demonstrates that the space occupied by continuous manufacturing is four times less than the space occupied by batch manufacturing. This is due to the fact that less space is required for production equipment and support equipment, as well as the fact that continuous manufacturing does not require an intermediate product warehouse. The space required for offices remains unchanged.

Table 3 Building of Batch and Continuous Manufacturing (24)

	Batch Manufacturing (m^2)	**Continuous Manufacturing (m^2)**
Process equipment	5940	1000
Infrastructure Space	2454	1000
Walk Areas	1360	400
Warehouse	1282	422
Office	1188	1188
Total	**12224**	**3950**

3.1.4 Quality, safety and technical considerations

The traditional tests carried out at the end of batch manufacturing are insufficient to control continuous manufacturing because the traceability of the material throughout the production is a fundamental concern for product quality.(15,28) In continuous manufacturing the characterization of raw materials and intermediate product properties

is complex as it is difficult to define the start and end of each product batch. This is exceptionally challenging in low volume, low dose drugs due to the high quantity of excipients used. (29)

Advanced process control is fundamental to continuous manufacturing to ensure process performance and product quality. As part of the control strategy, process management using the PAT tool allows real-time monitoring of critical quality parameters during the process. (27) In the production of oral pharmaceutical forms, NIR is used to control the homogeneity of the blending of active substance and excipients. (18,30,31) In addition, the start and end of production can be minimized to reduce material loss and the costs involved.(31)

Although continuous manufacturing may seem safer than batch manufacturing, it is necessary to be aware of some potential hazards that would not be considered in batch manufacturing. For example, overfilling and over-pressurization of the system. To minimize any potential hazards that may occur, many equipment manufacturers are collaborating with the pharmaceutical industry. However, pharmaceutical companies consider that any technical challenges that may exist are not an obstacle to the implementation of continuous manufacturing.(9,32)

3.1.5 Knowledge and skills

The implementation of continuous manufacturing technology requires highly qualified personnel. However, few industries have implemented this type of production and the lack of personnel with the relevant skills and knowledge is evident in the labor market. The difficulty of finding highly qualified people is also seen in regulators, since continuous manufacturing requires people capable of understanding the data generated. Since the qualification of personnel is required, CM presents an opportunity to create jobs in the most diverse areas.(33–35) Inevitably, the adoption of continuous manufacturing will make many jobs obsolete, due to the automation of the processes, foreseeing a reduction of 50% of the operators needed to perform the same production process when compared with batch manufacturing. (34,36) The fact that the processes are more automated will also minimize human error, thus reducing the deviations caused by this root-case.

3.1.6 Business, operational and cultural challenges

Continuous manufacturing should be implemented in the early stages of drug development, as this would avoid the regulatory requirements to prove equivalence with current processes. In terms of biopharmaceuticals, it is more effective to implement continuous manufacturing in the clinical trial phases because biopharmaceuticals are more complex and highly process-dependent.(37,38) In addition, regulatory uncertainty has led to a conservative culture on the part of the industry, delaying investment in new technologies. Thus, mindsets and cultural changes within the pharmaceutical industry are required to alter the batch manufacturing philosophy. To implement new production technologies in the pharmaceutical industry, it is necessary to prove significant benefits that justify their implementation. Therefore, it is essential that international organizations share successful experiences in continuous manufacturing to increase confidence in this type of production among manufacturers. (9,35,38)

3.2 Economic evaluation

One of the determining factors for the adoption of a new manufacturing technology is the cost associated with this production modernization. Even if a new technology can result in lower manufacturing costs and/or products with higher quality standards, the industry should compare the cost associated with the current type of production with the costs and benefits that the new technology can provide. Industries need to be aware that the current manufacturing process uses an established capital of known equipment and methods. (39,40)

The costs and benefits associated with new technology will depend on the competitive structure of the market, regulatory conditions, and other key factors, suggesting that what may be beneficial for some industries, may not be so beneficial for others.

It is notable that although in most processes continuous manufacturing is more efficient in the pharmaceutical industry, industry experts state that in certain situations CM is less efficient when compared to Batch manufacturing. An example of such a situation is when a company needs to produce relatively small quantities of a product with a defined production schedule to ensure sufficient stock before the product's shelf life expires. In this case, the cost of set-up, clean-up and time associated with continuous manufacturing could outweigh any associated gains. (17) Several authors in recent years have developed formulas that allow other industries to evaluate if continuous manufacturing is an option to be considered. Matsunami et al., (41)developed a model to calculate the total cost associated with batch and continuous manufacturing, helping in the decision between the choice of continuous manufacturing and batch manufacturing. This model comprises four steps: operational cost evaluation, sensitivity analysis, evaluation, and interpretation. The authors consider that the decision to choose the best manufacturing process must consider the API price and the demand for the drug. Through the model developed, the authors found that for 5.0×10^7 tablets/year and a USD1,000/kg API price, batch manufacturing is economically preferable as long as the effective manufacturing is higher than 19 kg/h, i.e., products with lower API price and high demand (e.g., generic drug products) or products with low demand and high API price (e.g., orphan drugs), continuous manufacturing was preferred when compared to batch manufacturing.(41)

On the other hand, the Schaber et al (17), compared the costs of producing tablets from an organic intermediate using batch and continuous manufacturing. Taking into account capital and operating costs (raw materials, labor, quality assurance, utilities and waste disposal costs), they concluded that continuous manufacturing would be the most economically advantageous manufacturing method showing gains of up to 30% if the cost of the organic intermediate was below the USD3,000/kg. Considering the two studies presented above, we can conclude that continuous manufacturing would be the most advantageous type of production. However, both batch manufacturing and continuous manufacturing are considered great tools within the pharmaceutical industry, and both have their ups and downs depending on the needs of pharmaceutical manufacturers and consumers.

3.3 Current worldwide implementation

In recent years, several companies have implemented continuous manufacturing as a production option. Companies such as Vertex Pharma, Eli Lilly and Pfizer were the first companies to implement this type of production and to obtain FDA approval for certain drugs produced. (12)

In Switzerland, Novartis created Continuous Pharmaceuticals to support the design of continuous manufacturing equipment. In South Korea, SK Biotek introduced continuous manufacturing to replace many batch manufacturing processes. (12)

In Table 4 shows some of the initiatives that these companies have developed.

Table 4 Initiatives from Major pharmaceutical Companies in continuous manufacturing of drug product. (12)(42)

Company	Initiatives
Hovione	Hovione and Vertex Pharma have teamed up to set a continuous manufacturing facility at the former's site in New Jersey, US. In 2017, Hovione has installed continuous manufacturing in New Jersey site.
Eli Lilly and Company	Introduced continuous manufacturing for drug ingredients and pharmaceuticals. In 2017, obtained FDA approval for breast cancer medication produced using continuous manufacturing. Eli Lilly became the first in Japan to obtain PMDA approval for continuous manufacturing of a new pharmaceutical product.
Pfizer Inc.	In 2018, obtained FDA approval for acute myeloid leukemia treatment agent produced using continuous manufacturing. In collaboration with GEA, developing portable facility for continuous manufacturing of solid dose preparations.

Company	Initiatives
Novartis International AG	Developing continuous manufacturing systems through joint research with MT (Novartis-MIT Center for Continuous Manufacturing). Aiming to realize "end-to-end" facilities by systematizing processes, from raw material input through to synthesis and drug formulation, into a coherent whole. Established continuous pharmaceuticals to promote the development and introduction of continuous manufacturing systems.
SK Biotek Co. Ltd	Has the system for systematic and coherent implementation of catalyst development, process development, and engineering. Also in continuous manufacturing, pursuing development of pharmaceutical manufacturing processes through to commercial operation of facilities.

Currently there are six approved commercial pharmaceutical products produced via continuous processes on the market, as can see in table 5.

Table 5 Marketed Drugs Approved for Continuous Manufacturing. (31,34,43)**.**

Year Approved	Drug	Pharma Company	Therapeutic Indication	FDA	EMA	PMDA (Japan)
2015	Orkambi	Vertex Pharmaceuticals	Cystic Fibrosis	X	X	
2016	Prezista	Jonhson & Jonhson	HIV	X		X
2017	Verzenio	Eli Lilly	Metastic Breast Cancer	X		X
2018	Symdeko	Vertex Pharmaceuticals	Cystic Fibrosis	X	X	
2018	Daurismo	Pfizer	Acute Myelocytic Leukemia	X		
2019	Trikafta	Vertex Pharmaceuticals	Cystic Fibrosis	X		
*	Tramacet	Janssen Pharmaceuticals	Pain			X

* Information not available

In July 2015, Vertex Pharmaceutcials obtained FDA approval for the continuous manufacturing of the drug Orkambi®, used to treat cystic fibrosis. The same company released two more drugs produced by CM, used for the treatment of cystic fibrosis (Symdeko® and Trikafta®).(8,31,41)

In early 2016 the FDA approved, for the first time a change in production method from batch to continuous manufacturing for the manufacturing of the protease inhibitor Prezista® (Darunavir) used in the treatment of HIV-1 infection (7,8)

Eli Lilly and Pfizer has joined the market of pharmaceutical CM with Verzenio® and Daurismo®, respectively. Verzenio® was approved for metastatic breast cancer and Daurismo® for acute myelocytic leukemia. (8,31,34)

The changing attitude of branded drug companies to CM has caused other companies to have an interest in this type of production. Companies like Dr. Reddy's, Mylan Pharmaceuticals and Aurobindo Pharma are investing in continuous manufacturing lines in India. (8,43)

4 Conclusions and Future Perspective

Although the initial investment to substitute batch manufacturing with continuous manufacturing is considerable, this project demonstrates that continuous manufacturing offers notable cost savings as there is a reduction in waste, a decrease in deviating batches, a decrease in failures due to manpower and a smaller occupation of space. Therefore, the benefit of implementing continuous manufacturing may compensate the initial cost invested. However, continuous manufacturing may not always be beneficial for the pharmaceutical industry. It is necessary to consider the API cost and the demand for the product, as well as to evaluate in more detail the needs of each pharmaceutical industry taking into consideration the type of business of the company.

Currently, industries such as Hovione, Pfizer, Eli Lilly and Company, Novartis International AG e SK Biotek Co. Ltd, consider continuous manufacturing as a production option. There are currently (as of June 2021) six FDA approved commercial pharmaceutical products on the market produced via continuous processes, namely Orkambi, Prezista, Verzenio, Symdeko, Daurismo, and Trikafta.

Pharmaceutical industries and regulators recognize the benefits of continuous manufacturing but there are still a number of big challenges that need to be overcome. Perhaps these challenges can be seen as opportunities for growth, risking revolutionizing pharmaceutical production with CM. Ultimately, the world would benefit from greater responsiveness to drug shortages and pandemics, increasing access to life-saving medicines, while contributing to environmental conservation.

It is expected that, in a near future, most pharmaceutical industries (both branded and generic) will adopt continuous manufacturing because of its cost-effectiveness, drastically reducing human intervention and production time. In addition, continuous manufacturing offers superior quality with minimal batch-to-batch variability. Regulatory organizations such as the FDA and EMA are also expected to establish strict regulations for manufacturers to follow and pharmacopoeias are expected to be amended to take into account continuous manufacturing technology.

5 References

1. Korhonen O. Continuous pharmaceutical manufacturing. Pharmaceutics. 2020;12(10):1–2.

2. Burcham CL, Florence AJ, Johnson MD. Continuous manufacturing in pharmaceutical process development and manufacturing. Annu Rev Chem Biomol Eng. 2018;9:253–81.

3. Vervaet C, Remon JP. Continuous granulation in the pharmaceutical industry. Chem Eng Sci. 2005;60(14):3949–57.

4. Roggo Y, Pauli V, Jelsch M, Pellegatti L, Elbaz F, Ensslin S, et al. Continuous manufacturing process monitoring of pharmaceutical solid dosage form: A case study. J Pharm Biomed Anal. 2020;179:112971.

5. Cole KP, Johnson MD. Continuous flow technology vs. the batch-by-batch approach to produce pharmaceutical compounds. Expert Rev Clin Pharmacol. 2018;11(1):5–13.

6. Lee SL, O'Connor TF, Yang X, Cruz CN, Chatterjee S, Madurawe RD, et al. Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production. J Pharm Innov. 2015;10(3):191–9.

7. Blackshields CA, Crean AM. Continuous powder feeding for pharmaceutical solid dosage form manufacture: a short review. Pharm Dev Technol. 2018;23(6):554–60.

8. Helal NA, Elnoweam O, Eassa HA, Amer AM, Eltokhy MA, Helal MA, et al. Integrated continuous manufacturing in pharmaceutical industry: current evolutionary steps toward revolutionary future. Pharm Pat Anal. 2019;8(4):139–61.

9. Qiao Z, Wang Z, Zhang C, Yuan S, Zhu Y, Wang J. Perspectives on the Continuous Manufacturing of Powder-Based Pharmaceutical Processes. AIChE J. 2016;59(4):215–28.

10. Infarmed [Internet]. [cited 2021 Apr 2]. Available from: https://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso-

humano/inspecao-medicamentos/materias-primas

11. Plumb K. Continuous processing in the pharmaceutical industry: Changing the mind set. Chem Eng Res Des. 2005;83(6 A):730–8.

12. Inada Y. Continuous Manufacturing development in Pharmaceutical and Fine Chemicals Industries. 2019;(December):1–7.

13. Kleinebudde P, Khinast J, Rantanen J. Continuous Manufacturing of Pharmaceuticals. Vol. 53, Journal of Chemical Information and Modeling. Wiley; 2017. 1–50 p.

14. Rathore AS, Agarwal H, Sharma AK. Preparative Biochemistry and Biotechnology Continuous Processing for Production of Biopharmaceuticals. (February 2015):37–41.

15. Chaudhary RS, Pazhayattil A, Spes J. Continuous Manufacturing: A Generic Industry Perspective. Pharm Tech [Internet]. 2017;(May):1–5. Available from: http://www.pharmtech.com/continuous-manufacturing-generic-industry-perspective

16. Djuric D, Kleinebudde P. Impact of Screw Elements on Continuous Granulation With a Twin-Screw Extruder. 2008;97(11):4934–42.

17. Schaber, S., Gerogiorgis, D., Ramachandran, R., Evans, J., Barton, P., Trout B. Economic analysis of integrated continuous and batch pharmaceutical manufacturing: a case. 2016;10083–92.

18. Vargas JM, Nielsen S, Cárdenas V, Gonzalez A, Aymat EY, Almodovar E, et al. Process analytical technology in continuous manufacturing of a commercial pharmaceutical product. Int J Pharm. 2018;538(1–2):167–78.

19. Nasr MM, Krumme M, Matsuda Y, Trout BL, Badman C, Mascia S, et al. Regulatory Perspectives on Continuous Pharmaceutical Manufacturing : Moving From Theory to Practice . September 26-27 , 2016 , International Symposium on the Continuous Manufacturing o ... Regulatory Perspectives on Continuous Pharmaceutical Manufacturing. J Pharm Sci. 2017;(June).

20. Allison G, Cain YT, Cooney C, Garcia T, Bizjak TG, Holte O, et al. Regulatory and quality considerations for continuous manufacturing May 20-21, 2014

continuous manufacturing symposium. J Pharm Sci. 2015;104(3):803–12.

21. Allison G, Cain YT, Cooney C, Garcia T, Gooen T, Holt O, et al. White Paper 3 -- Regulatory and Quality Considerations for Continuous Manufacturing. Int Symp Contin Manuf Pharm. 2014;

22. FDA. U.S. Food and Drug Administration (FDA). Quality Considerations for Continuous Manufacturing Guidance for Industry DRAFT GUIDANCE. Ind Draft Guid. 2019;(February):1–27.

23. OConnor T, Lee S. Emerging technology for modernizing pharmaceutical production: Continuous manufacturing. Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice: Second Edition. Elsevier Inc.; 2017. 1031–1046 p.

24. Wilbura HR. The Business Case for Continuous Mnufacturing of Pharmaceuticals. 2010.

25. Randi Hermandez. Contnuous Manufacturing: A Changing Processing Paradigm. BioPharm. 2015;28(4):20–7, 41.

26. Hinz DC. Process analytical technologies in the pharmaceutical industry : the FDA ' s PAT initiative. 2006;1036–42.

27. Román-Ospino AD, Singh R, Ierapetritou M, Ramachandran R, Méndez R, Ortega-Zuñiga C, et al. Near infrared spectroscopic calibration models for real time monitoring of powder density. Int J Pharm. 2016;512(1):61–74.

28. Tian G, Koolivand A, Arden NS, Lee S, O'Connor TF. Quality risk assessment and mitigation of pharmaceutical continuous manufacturing using flowsheet modeling approach. Comput Chem Eng. 2019;129:106508.

29. Matsunami K, Nagato T, Hasegawa K, Sugiyama H. A large-scale experimental comparison of batch and continuous technologies in pharmaceutical tablet manufacturing using ethenzamide. Int J Pharm. 2019;559(December 2018):210–9.

30. Vargas JM, Roman-Ospino AD, Sanchez E, Romañach RJ. Evaluation of Analytical and Sampling Errors in the Prediction of the Active Pharmaceutical Ingredient Concentration in Blends From a Continuous Manufacturing Process.

J Pharm Innov. 2017;12(2):155–67.

31. Vanhoorne V, Vervaet C. Recent progress in continuous manufacturing of oral solid dosage forms. Int J Pharm. 2020;579(December 2019):119194.

32. Byrn S, Futran M, Thomas H, Jayjock E, Maron N, Meyer RF, et al. Achieving continuous manufacturing for final dosage formation: Challenges and how to meet them May 20-21, 2014 continuous manufacturing symposium. J Pharm Sci. 2015;104(3):792–802.

33. Poechlauer P, Manley J, Broxterman R, Gregertsen B, Ridemark M. Continuous processing in the manufacture of active pharmaceutical ingredients and finished dosage forms: An industry perspective. Org Process Res Dev. 2012;16(10):1586–90.

34. Badman C, Cooney CL, Florence A, Konstantinov K, Krumme M, Mascia S, et al. Why We Need Continuous Pharmaceutical Manufacturing and How to Make It Happen. J Pharm Sci. 2019;108(11):3521–3.

35. Baxendale IR, Braatz RD, Hodnett BK, Jensen KF, Johnson MD, Sharratt P, et al. Achieving Continuous Manufacturing: Technologies and Approaches for Synthesis, Workup, and Isolation of Drug Substance May 20–21, 2014 Continuous Manufacturing Symposium. J Pharm Sci. 2015;104(3):781–91.

36. Shanley A. Building a Continuous Processing CultureNo Title [Internet]. 2017 [cited 2021 Jun 3]. Available from: https://www.pharmtech.com/view/building-continuous-processing-culture

37. Gottlieb S. FDA statement on FDA's modern approach to advanced pharmaceutical manufacturing [Internet]. [cited 2021 Jun 3]. Available from: https://www.fda.gov/news-events/press-announcements/fda-statement-fdas-modern-approach-advanced-pharmaceutical-manufacturing

38. Martin J. Is Continuous Manufacturing Right For Your Drug Product? [Internet]. 2019 [cited 2021 Jun 3]. Available from: https://www.pharmaceuticalonline.com/doc/is-continuous-manufacturing-right-for-your-drug-product-0001

39. Zhang H, Lakerveld R, Heider PL, Tao M, Su M, Testa CJ, et al. Application of

continuous crystallization in an integrated continuous pharmaceutical pilot plant. Cryst Growth Des. 2014;14(5):2148–57.

40. Cervera-Padrell AE, Skovby T, Kiil S, Gani R, Gernaey K V. Active pharmaceutical ingredient (API) production involving continuous processes - A process system engineering (PSE)-assisted design framework. Eur J Pharm Biopharm. 2012;82(2):437–56.

41. Matsunami K, Miyano T, Arai H, Nakagawa H, Hirao M, Sugiyama H. Decision Support Method for the Choice between Batch and Continuous Technologies in Solid Drug Product Manufacturing. 2018;

42. Hovione [Internet]. Available from: https://www.hovione.com/press-room/article/hovione-build-us-plant-vertexs-cystic-fibrosis-drugs

43. Pharmaceutical Technology- Article [Internet]. [cited 2021 Apr 2]. Available from: https://www.pharmaceutical-technology.com/comment/continuous-manufacturing-of-biologics-2020/