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An audit of pharmaceutical continuous manufacturing regulatory submissions and outcomes in the US

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ABSTRACT

Continuous manufacturing (CM) sends materials directly and continuously to the next step of a process, eliminating hold times and reducing processing times. The potential benefits of CM include improved product quality, reduced waste, lower costs, and increased manufacturing flexibility and agility. Some pharmaceutical manufacturers have been hesitant to adopt CM owing to perceived regulatory risks such as increased time to regulatory approval and market entry, more difficulty submitting postapproval changes, and higher inspectional scrutiny. An FDA self-audit of regulatory submissions in the U.S. examined the outcomes, at approval and during the product lifecycle, of continuous manufacturing applications as compared to traditional batch applications. There were no substantial regulatory barriers identified for CM applications related to manufacturing process changes or pre-approval inspections. CM applicants had relatively shorter times to approval and market as compared to similar batch applications, based on the mean or median times to approval (8 or 3 months faster) and marketing (12 or 4 months faster) from submission, translating to an estimated $171–537 M in early revenue benefit.

1. Introduction

Continuous manufacturing (CM) is a technology that sends materials produced during each process step directly and continuously to the next step for further processing. In such a process, input materials are continuously fed into production and transformed, and processed output materials are continuously removed. CM has been adopted in many industries (e.g., petroleum, commodity chemicals), while the pharmaceutical industry has been slower to adopt CM (Lee et al., 2015; Rossi, 2022). The U.S. landscape of prescription drug products made using a CM process was roughly $3.09B in 2020 (Fig. 1), representing a small but growing portion of the $172B total market for branded, solid oral prescription drugs. The leading firm in the CM sector captures around 65% of total sales, with 20% of sales captured by the next largest firm. Many have pointed to the slow adoption of advanced manufacturing technologies, including CM, as one of the reasons that the pharmaceutical industry has not achieved the consistent six sigma manufacturing capability (i.e., <3.4 errors per million opportunities) common in other industries (Politis and Rekkas, 2011; Yu and Kopcha, 2017).

The United States Food and Drug Administration (FDA) has long championed the development and implementation of advanced manufacturing technologies like CM for drug substances and finished drug products because of the potential to improve product quality and reliability, lower manufacturing costs, reduce waste, decrease inventory, and increase manufacturing flexibility and agility in response to fluctuations in product demand. The cumulative effects of CM adoption could reduce or mitigate drug shortages (Lee et al., 2015). CM can be applied to all classes of products: new drugs submitted in New Drug Applications (NDAs) (Hernandez, 2015), generic drugs filed in Abbreviated New Drug applications (ANDAs) (Chaudhary et al., 2017), drug substances filed in Drug Master Files (DMFs) (Stauffer et al., 2019), biotechnology products filed in Biologics License Applications (BLAs) (Fisher et al., 2019), and nonprescription drugs (Griffin et al., 2010). There is now a rich source of scientific literature describing the benefits of CM in pharmaceutical manufacturing relating mostly to decreases in production/operating costs and improvements in product quality and reliability (Rossi, 2022; Badman et al., 2019). Perhaps most importantly for patients and consumers, CM has the potential to impact product availability; for example, by avoiding drug shortages due to manufacturing problems or expediting patient access through improved

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manufacturing agility and easier scale-up to commercial production (Miller et al., 2020; Maniruzzaman and Nokhodchi, 2017; Capellades et al., 2021).

The FDA's Center for Drug Evaluation and Research (CDER) has several visible commitments to facilitate the adoption of CM. Perhaps most visible is the *Draft Guidance for Industry: Quality Considerations for Continuous Manufacturing* published in 2019, which provides FDA's current thinking on the quality considerations for the continuous manufacturing of small molecule, solid oral drug products (FDA. Quality Considerations for Continuous Manufacturing Guidance for Industry. In:, 2019). CDER's Emerging Technology Program seeks to promote the adoption of innovative approaches to pharmaceutical product design and manufacturing, such as CM, through direct engagement with industry representatives (FDA. Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization Guidance for Industry. In:, 2017). Under this program, FDA staff and participants discuss, identify, and resolve potential technical and regulatory issues regarding the development and implementation of a novel technology prior to the filing of a regulatory submission. CDER approved the first application employing CM in 2015 following extensive engagement between the applicant and the Emerging Technology Program (Wahlich, 2021). CDER has funded a large and growing scientific knowledge base for CM fueled by intramural and extramural research on topics such as process modeling (Tian et al., 2019; Tian et al., 2021; Tian et al., 2017), crystallization (Acevedo et al., 2021; Acevedo et al., 2018; Hu et al., 2018; Hu et al., 2020; Liu et al., 2020; Domokos et al., 2020; Yang et al., 2017), formulation (Liu et al., 2019; Liu et al., 2017; Liu et al., 2019; Moreno et al., 2019; Park et al., 2018), bioprocesses (Hong et al., 2020; Trunfio et al., 2018), and integrated (i.e., inclusive of drug substance and drug product) continuous processes (Hu et al., 2020; Hu et al., 2020). Recognizing that global regulatory harmonization can be significant barrier to CM adoption, the FDA leads international regulators in developing a harmonized international guideline on CM (ICH Q13) to further lower regulatory uncertainty regarding implementation across multiple regulatory regions (ICH, 2021).

There are known perceptions in the pharmaceutical industry of regulatory barriers that reduce the attractiveness of advanced manufacturing technologies, such as CM (Mantle and Lee, 2020; Arden et al., 2021). Some key regulatory concerns relate to increased time to approval and market entry, more difficulty implementing and submitting postapproval changes, and increased inspectional scrutiny (Matsuda, 2019). While the benefits of CM adoption in the context of capital and operating expenditures have been explored extensively in the literature; regulators have not yet described or quantified the regulatory outcomes of products made using CM (Gupta et al., 2021; Matsunami et al., 2018; Jolliffe and Gerogiorgis, 2016; Schaber et al., 2011). Here we self-audit the approved U.S. regulatory submissions to CDER that employ CM and analyze the relevant regulatory outcomes, at approval and during the product lifecycle, as compared to applications that employ traditional batch processes by examining:

- Time to approval and market entry
- Manufacturing process changes reported in Annual Reports
- Manufacturing-related postapproval application supplements
- Pre-approval inspections

To the extent possible, we estimate the economic impact of time to approval and market entry to better inform strategic decisions regarding the adoption and implementation of CM.

2. Methods

2.1. Comparison datasets

Processes were deemed to be continuous if they met the description in the *Draft Guidance for Industry: Quality Considerations for Continuous Manufacturing*; i.e., an integrated process consisting of a series of two or more unit operations (FDA, 2019). At the start of 2022, there were six approved applications that utilize CM for their finished solid oral drug products (i.e., immediate release solid oral dosage form products, IR SODF); the first was approved in 2015. One application's product is approved to be made by either a batch or CM process, by the same firm.

To enable comparison, we used a set of approved comparator products manufactured using batch operations and meeting all of the following criteria: (i) subject of an NDA, (ii) approved within calendar years 2015–2020 (with the exception described below), and (iii) an IR SODF. These criteria resulted in a comparator dataset consisting of 134 NDAs. Subsets of this dataset, based on additional criteria, were used for comparison, as described below.

2.2. Time to approval and market Entry, associated revenue potential

Market landscape analysis of CM products was performed using data derived from IQVIA National Sales Perspectives (NSP), 2014–2020. The revenues associated with time to approval and marketing for the original applications were calculated by multiplying the difference in time and the average monthly sales (across 12 months) in 2020 from IQVIA NSP for the CM products. For this purpose, the CM product initially approved

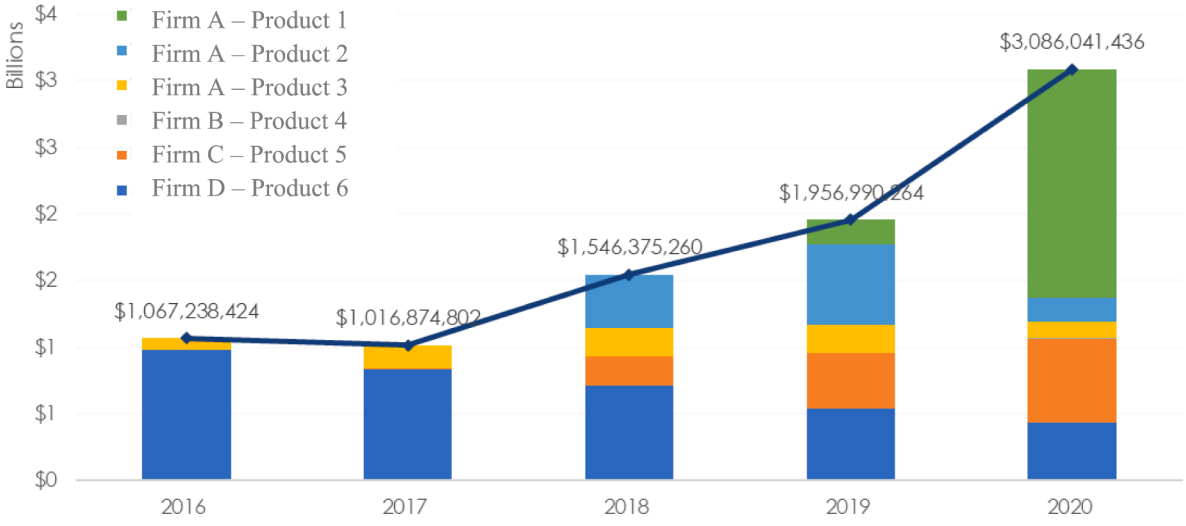

Fig. 1. Annual sales of products made using CM 2016–2020.

with a batch process in 2006 was excluded (n = 5). Annual sales were inflation adjusted to 2020 dollars using the annual average Consumer Price Index for All Urban Consumers (CPI-U). Approval times (in months) were calculated from the date of first FDA application submission to original application approval. Marketing dates (month of first recorded sales) were obtained by matching application products to products in IQVIA NSP and extracting the date of the first marketed product associated with that application. Applications for which we could not derive marketing dates (n = 16) were removed from the time-to-marketing estimates. A review cycle was considered complete if the review ended in either a Complete Response, Approval, or Tentative Approval action.

2.3. Annual report text mining

The regulation at 21 CFR 314.81(b)(2) requires an applicant to submit an annual report within 60 days of the anniversary of U.S. approval for every NDA. Text analysis of Annual Reports was conducted using a Python script to count the occurrence of the term "manufacturing process change" in electronic common technical document modules 1.13.5, 1.13.6, and 1.13.7 (FDA, 2020). Since the earliest approval of a CM application occurred in 2015, Annual Reports were text-mined for 2016–2020, allowing for a maximum of five Annual Reports for the earliest approved applications. Of the 134 batch applications, 20 were approved between November 2019 and September 2020 and no Annual Reports had yet been submitted for these applications at the time of analysis.

2.4. Postapproval application supplements and pre-approval inspections

Post-market application supplements related to chemistry, manufacturing, and controls (CMC) were counted and changes characterized as "manufacturing process changes" were reported. For the product made with either a batch or CM process, inspections and supplements specific to the type of process were used for analysis. Pre-Approval Inspection (PAI) reports for the finished drug product manufacturer were reviewed (FDA, 2017). Since inspection findings could focus on multiple products, only those deficiencies specific to the product in the analysis in the inspection report (discussion items) and on the Form FDA 483 (inspection observations) were quantified.

3. Results

3.1. Time to approval and market entry

Perhaps the key risk for adopters of CM is the risk of delayed product approval, as this would fundamentally impact revenue and profit projections. When examining the five products made using CM at the time of original NDA approval, we observed that all were approved in the first review cycle, ahead of the User Fee goal date with no Complete Response letters issued. On average, CM applications were approved nine months faster than batch applications and entered the market twelve months faster after regulatory submission and three months faster after approval than batch applications (Table 1). However, the mean timelines associated with batch applications were heavily skewed by outlier products with long approval times. When looking at median approval timelines, CM applications were approved three months faster than batch applications and reached marketing four months and one month faster after regulatory submission and approval, respectively (Table 1). Patients received earlier access to CM products and, as the average monthly revenue of CM products in 2020 was $42.9 M, companies selling CM products realized an estimated early revenue benefit of $171 to 537 M, based on the median or mean time to marketing from submission, as compared to batch products.

Table 1
Mean and median time to approval and marketing and the number of Complete Response (CR) letters and review cycles of batch and CM applications.

	Batch (n = 135)	Continuous Manufacturing (n = 5)
Time to Approval (mos.)		
Mean	15 ± 21	6.00 ± 2.35
Median	10 [8, 12]	7 [4, 8]
Time to Marketing from Submission (mos.)		
Mean	19 ± 23	6.40 ± 2.30
Median	12 [8.50, 18]	8 [5, 8]
Time to Marketing from Approval (mos.)		
Mean	3.49 ± 6.24	0.40 ± 0.55
Median	1 [0.50, 3]	0 [0, 1]
CRs / Application		
Mean	0.096 ± 0.32	0
Median	0 [0, 0]	0 [0, 0]
Review Cycles		
Mean	1.12 ± 0.35	1
Median	1 [1, 1]	1 [1, 1]

Values in [] represent the interquartile range (IQR) while values following averages (±) are standard deviations.

3.2. Manufacturing process changes reported in annual reports

Annual Reports must include, among other elements, a full description of CMC (chemistry, manufacturing, and controls) changes not required to be submitted in an application supplement. As these CMC changes could include changes to the manufacturing process, we reasoned that Annual Reports may reflect the regulatory burden related to, and the need for, postapproval process changes. Since there were too many Annual Reports to audit manually, we employed text mining for the term "manufacturing process change." For the 114 batch applications with 309 Annual Reports (20 batch applications do not yet have an Annual Report), there were 33 mentions of "manufacturing process change" and we observed that the *drug product process* was changed in 21 of these annual reports (Table 2). For the five applications for products made only through CM with 12 Annual Reports, there were no mentions of the term "manufacturing process change." Notably, the one application product made by both batch and CM had 5 total mentions of the term in Annual Reports, and only one related to the CM process (data not shown).

3.3. Number of postapproval application supplements

Due to the manageable volume, we manually audited postapproval application supplements for CM products. For comparative purposes, we noted: (i) only one firm manufactures three CM products, (ii) only three firms manufacture an approved product using CM and other approved products using batch manufacturing, and (iii) only one firm manufactures an FDA-approved product using both CM and batch manufacturing (for the same strength of the product). As summarized in Table 3:

- Group 1: The only firm that manufactures three CM products submitted 10 postapproval supplements. Of the 134 applications that met the batch product comparator criteria, only three firms had more than one approved product within the five-year timeframe of this study and none of those three firms make any approved products using CM. Collectively, these three batch comparator firms submitted 26 postapproval supplements for their six batch products.
- Group 2: The only three firms that manufacture approved products using CM and other approved products using batch manufacturing

Table 2
Manufacturing Process Changes Reported in Annual Reports 2016–2020.

Source	Annual Reports	Total "Manufacturing Process Change" Mentions	"Manufacturing Process Change" Mentions per Annual Report	Total Drug Product Process Changes	Drug Product Process Changes per Annual Report
Batch Applications (n = 114)	309	33	0.11	21	0.07
CM Applications (n = 5)	12	0	0.00	0	0.00

collectively submitted 5 supplements for their three CM products and 18 supplements for their nine batch products.

- Group 3: The only firm that manufactures an FDA-approved product made using both CM and batch manufacturing submitted three supplements for their CM product strength and eleven supplements for all other product strengths (i.e., batch products). For this firm, it is important to note that the batch process was approved almost a decade before the CM process (2006 and 2016, respectively).

Approximately 30% of postapproval supplements for all applications (batch and CM) were related to the manufacturing process; a notable observation is that we did not find changes in equipment, processing conditions, or batch size in supplements for CM applications, though we did in supplements for batch applications. This observation may indicate the inherent flexibility of CM processes.

3.4. Pre-approval inspections

We also manually audited pre-approval inspection documents. Related to product-specific pre-approval inspections, as summarized in Table 3:

- Group 1: The only firm that manufactures three CM products was subject to three pre-approval inspections during the original application review (an inspection was not conducted for one product, but two were conducted for another). The three batch comparator firms described above in 3.3 were subject to five pre-approval inspections for their six batch applications.
- Group 2: The only three firms that manufacture approved products using CM and other approved products using batch manufacturing were collectively subject to three pre-approval inspections for their three CM products and three pre-approval inspections for their 9 batch products.
- Group 3: The only firm that manufactures an FDA-approved product made using both CM and batch manufacturing was subject to one pre-approval inspection for the application implementing the batch process and one pre-approval inspection for the application supplement implementing the CM process.

The majority of batch and nearly all CM products were subject to a pre-approval inspection; a notable observation is that we did not find process-related inspection observations for batch products, though we did for CM products (primarily related to oversight of manufacturing process and controls). This observation may indicate a difference in inspection focus between batch and CM processes.

4. Discussion

Many studies of CM implementation have focused on estimating capital and operating costs of facilities, considering varying raw material costs, production methods, and levels of drug demand (Matsunami et al., 2018; Jolliffe and Gerogiorgis, 2016; Schaber et al., 2011). An influential study on the economics of CM by Schaber et al. describes potential CM operating and capital cost savings compared to traditional batch operations to vary widely (6%-40% and 20%-75%, respectively) depending on initial assumptions including the costs of chemical intermediates and type of CM process (Schaber et al., 2011). In this self-audit of continuous manufacturing regulatory submissions in the U.S., we considered key regulatory concerns among pharmaceutical manufacturers related to the adoption of advanced manufacturing technologies; namely, increased time to approval and market entry, more difficulty implementing and submitting postapproval changes, and higher inspectional scrutiny. In sum, the findings of this audit do not indicate higher risks to regulatory submissions or outcomes for CM applications as compared to batch applications.

We observed that CM applicants achieved faster approvals and market entry based on average time to approval and marketing from submission than their batch counterparts. There was also a comparative advantage in reaching the market faster following approval. CM products reached the marked approximately 1–3 months faster after approval than batch applications. While there are multiple drivers determining the time between approval and marketing, supply chain considerations and manufacturing scale-up are often bottlenecks. For example, batch manufacturers typically need to utilize new equipment, update processes, and complete process performance qualification for the commercial-scale process. CM operations, by design, have fewer process and equipment considerations in reaching commercial-scale operations, as changes to accommodate commercial scale typically involve increasing run time or line rate, while other manufacturing elements (e.g., process parameters, controls, and equipment) are held consistent. The decrease in time to market after approval, alone, accounts for $42.9–128.4 M of estimated early revenue benefit as compared to batch processes.

While there are many elements of application review that impact the final approval decision, it is important to note that one driver supporting first-cycle approvals of CM products is the interaction with CDER's Emerging Technology Program. All CM applicants in this audit engaged with the Emerging Technology Program to obtain answers to their questions during development and prepare for NDA submission (O'Connor et al., 2016). Though this level of regulatory engagement on CM products will not continue indefinitely as CM technology matures, engagement with the Emerging Technology Program has been a clear advantage for the adoption and implementation of CM. It is important to note that four of the six approved CM applications were granted Breakthrough Therapy designation which expedited their review timeline (Corrigan-Curay et al., 2018). This factor was not considered for the purposes of our analysis and these approvals showed the FDA's ability to approve CM products meeting or exceeding even expedited review timelines.

Text mining of Annual Reports of approved original applications found no instances of the term "manufacturing process change" for CM applications in the five years since the first CM approval (Table 2). For batch processes, we observed that mentions of the term decreased over time from the date of approval as one might expect as a batch process matures, supporting the term's usage as an indicator of process robustness. Of course, usage of this term is an imperfect indicator of process robustness; for example, it is not a structured regulatory term and some changes detected through text mining in the batch applications were associated with aspects outside of the intrinsic process (e.g., analytical methods, container closure manufacturers). When looking at

Table 3
Batch and CM postapproval supplements and pre-approval inspections 2016–2020.

Sets	Source	Total Postapproval Supplements	Postapproval Supplements per Year Since Approval	Total Process Related Postapproval Supplements	Process Related Postapproval Supplements per Year Since Approval	Total Pre-approval Inspections	Pre-Approval Inspections per Product
Group 1	3 CM Products From 1	10	1.25	5	0.63	3	1
Comparators	CM-Only Firm						
	6 Batch Products From 3 Batch-Only Firms	26	1.13	7	0.30	5	0.83
Group 2	3 CM Products From 3 Firms	5	0.56	1	0.11	3	1
Comparators	9 Batch Products From Same 3 Firms	18	1	7	0.39	3	0.33
Group 3	1 Product Made by CM	2	0.50	1	0.25	1	1
Comparators	Same Product Made by Batch by Same Firm	11	0.79	2	0.14	1	1

postapproval application supplements, there was not a substantial difference in the number of process changes reported in application supplements between batch and CM applicants. However, we observed that CM applicants reported no changes related to equipment, processing conditions, or batch size. CM processes are often designed to have inherent flexibility to make certain process changes after approval (e.g., run time, process parameters) to modify outputs (e.g., scale) without the need for a postapproval supplement.

While the majority of batch products used for comparison were subject to pre-approval inspections, a pre-approval inspection was conducted for nearly 100% of the CM products. CM applications had more process-related issues observed during inspection than batch applications. We hypothesize that a reason for these differences may stem from the fact that the FDA determines the need for a pre-approval inspection, in part, by considering whether previous inspections and existing knowledge provide confidence that the facility can manufacture the drug in compliance with regulations and in conformance with application commitments. Since many CM facilities and processes are new, the FDA has relatively little existing knowledge of their ability to manufacture. On the other hand, facilities manufacturing batch products often have a deeper inspection history. This inherent difference in existing knowledge may contribute to the differences in the number of inspections and an increased focus on manufacturing process and controls during inspections of CM facilities. It stands to reason that as FDA's confidence in manufacturers' capability to implement CM increases, the need for pre-approval inspections and the number of process-related issues observed during inspections at facilities already using CM should lessen. Most importantly, pre-approval inspections did not adversely impact the application approval timelines for CM applications, as all were approved in the first review cycle.

5. Conclusions

This FDA self-audit of continuous manufacturing regulatory submissions and outcomes identified no substantial barriers associated with common regulatory interactions (e.g., time to approval, postapproval change reporting, inspectional scrutiny) related to implementation of CM as compared to batch manufacturing. There are potential regulatory (e.g., manufacturing process scale-up flexibility) and clear economic (e.g., time to approval, time to market) advantages observed for applications using CM. Products of CM tended to reach the market sooner after regulatory filing, translating to earlier patient access to medicines and a potential $171–537 M in early revenue benefit.

CRediT authorship contribution statement

Adam C. Fisher: Conceptualization, Methodology, Visualization, Writing – original draft. **William Liu:** Methodology, Investigation, Formal analysis, Writing – review & editing. **Andreas Schick:** Writing – review & editing, Supervision. **Mahesh Ramanadham:** Conceptualization, Methodology, Visualization, Writing – review & editing. **Sharmista Chatterjee:** Methodology, Investigation, Formal analysis, Writing – review & editing. **Raphael Brykman:** Methodology, Investigation, Formal analysis, Writing – review & editing. **Sau L. Lee:** Conceptualization, Writing – review & editing, Supervision. **Steven Kozlowski:** Conceptualization, Writing – review & editing. **Ashley B. Boam:** Conceptualization, Writing – review & editing. **Stelios Tsinontides:** Conceptualization, Writing – review & editing, Supervision. **Michael Kopcha:** Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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