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COMMENTARY

Reimagining drug manufacturing paradigm in today's pharmacy landscape

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ABSTRACT

The coronavirus disease 2019 pandemic has escalated the ongoing problem of critical medication shortages, which has serious implications for the health of our patients. Currently, active pharmaceutical ingredients (APIs) are synthesized in large-scale batch operations and shipped to drug product manufacturers, where they are produced on a large scale at centralized facilities. In the centralized drug manufacturing process, the formulation components, operations, and packaging are structured to favor long-term storage and shipment of resultant medicines to the point of care, making this process vulnerable to supply chain disruptions. We propose a rethinking of the drug manufacturing paradigm with an upgraded pharmaceutical compounding-based manufacturing paradigm. This paradigm will be based on integration of continuous manufacturing of APIs and manufacturing of medicines at the point of care with application of machine learning, artificial intelligence, and 3-dimensional printing. This paradigm will support implementation of precision medicine and customization according to patients' needs. The new model of drug manufacturing will be less dependent on the supply chain while ensuring availability of medicines in a cost-effective manner.

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Medication (“drug”) shortages have long been recognized as a critical issue and, despite advancements in both manufacturing and distribution, continue to impact health care delivery within the United States.¹ The Center for Drug Evaluation and Research defines a drug shortage as “a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug.”² The impacts of such shortages are significant and have been associated with increased economic burden, decreased patient substantial, and worsened patient outcomes.² It has been reported that the impact of drug shortages within the United States had led to medication error rates between 1% and 5% in addition to creating unsafe conditions for patients.³ In a survey of pharmacy directors within the United States, researchers identified treatment failures, medication errors, serious adverse effects, readmission rates, and treatment delays as consequences of drug shortages within acute care settings.⁴

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Drug shortage issues are complex and multifaceted. The Food and Drug Administration (FDA) has reported issues related to manufacturing and raw material availability as two of the largest causes of drug shortages in the United States.¹ Manufacturing delays, decreased capacity, product discontinuation, and loss of manufacturing sites also play a role.¹ Furthermore, vulnerabilities in the U.S. drug supply chain have resulted from a heavy dependence on foreign sourcing for both medication components and finished products, with an estimated 72% of all active pharmaceutical ingredient (API) manufacturers located overseas.⁵ More recently, the coronavirus disease 2019 (COVID-19) pandemic has exacerbated these problems by increasing vulnerability to supply chain disruptions.⁶

By design, traditional centralized manufacturing is set up to have every step fixed (not readily adaptable to formulation or process modifications), which makes mitigating many drug shortage issues challenging. As part of the Strategic Plan for Preventing and Mitigating Drug Shortages, FDA outlined 2 goals, including (1) improving the mitigation response to imminent or existing shortages and (2) implementing strategies for the long-term prevention of shortages by focusing on root causes. This plan also sought to identify ways in which to incentivize innovation and promote and sustain manufacturing and product quality improvements.⁷

Key Points**Background:**

- The centralized (traditional) drug manufacturing process is vulnerable to supply chain disruptions.
- In the traditional drug manufacturing process, operations, formulation components and packaging are structured to favor long-term formulation storage and shipment to the point of care.

Findings:

- We propose an upgraded pharmaceutical compounding-based drug manufacturing paradigm that will take place at the point of care.
- The new process will be based on integration of continuous manufacturing of active pharmaceutical ingredients with application of machine learning, artificial intelligence and 3-dimensional printing technologies.
- The new paradigm will support implementation of precision medicine and customization according to patients needs.

In this article, we propose a new drug manufacturing paradigm. In doing so, we describe the shortcomings of current manufacturing practices, summarize opportunities for using emerging technological advancements such as 3-dimensional (3D) printing and artificial intelligence, and highlight how upgrading pharmaceutical compounding may assist in rectifying drug shortage issues. This article focuses on efforts to manufacture nonsterile products intended for oral administration, considers the factors that necessitate an overhaul of the drug manufacturing paradigm in the United States, and discusses changes necessary to implement the proposed new paradigm.

Shortcoming of the current drug manufacturing paradigm

The current drug manufacturing paradigm is heavily dependent on supply chains to meet all the requirements for centralized mass production of medicines. After production, medicines are subsequently stored and shipped to the point of patient care. Owing to the typical long time before medicines will reach patients, formulation materials and packaging materials are carefully selected to ensure that the quality of medicines throughout the time course of production, transportation, and storage remains unchanged. These requirements at every stage of the current drug manufacturing paradigm contribute to its vulnerability to supply chain disruptions, which was escalated during COVID-19 pandemic, leading to drug shortages. Furthermore, a centralized medicine production paradigm is well suited for a one-size-fits-all approach to achieve production efficiency, leaving little room for personalized therapy. Given the rigidity of this model, opportunities for innovation customization and adaptability in challenging situations are very scarce. If emerging

technological advancements such as 3D printing,⁸ artificial intelligence,⁹ and pharmacogenomics¹⁰ will be fully integrated in pharmacy practice, then it is high time we re-imagined the drug manufacturing paradigm.

Overview of a new approach: Upgrading pharmaceutical compounding

Patients need reliable access to their medications, and medications must be made more accessible without increasing their cost. We envision a drug manufacturing paradigm that will make critical medicines available at the point of care through an upgraded compounding-based manufacturing paradigm (Figure 1). In this approach, APIs will be produced at regional facilities via continuously manufacturing processes and will be subsequently delivered to 503A compounding pharmacies for formulation and delivery to the patient. The formulation of APIs will adopt various technologies to improve precision and customization of medicines for each patient's unique situations. Medication customization can be achieved via 3D printing,⁸ as well as through other technologies such as Drop-on-Demand or Dropwise Additive Manufacturing of Pharmaceutical Products that involve depositing fluid formulations onto a substrate material in a dropwise fashion as needed.¹¹ These novel technologies can yield dosage forms that can be adjusted frequently, if necessary, depending on biofeedback data and patient preference using Big Data and artificial intelligence approaches.^{12,13}

The proposed manufacturing paradigm involves implementing smaller-scale compounding to overcome pitfalls associated with large-scale (mass production) drug manufacturing. Smaller-scale drug production (compounding-based approach) could also reduce the overall cost of manufacturing by decreasing the number of ingredients needed to formulate the product while shortening time-consuming steps in the manufacturing process. The requirement for extended shelf-life of products in centralized mass production manufacturing is not warranted in the envisioned smaller-scale production to meet demand at the point of care.

Patient access to medications could be improved by adaptability of the compounding-based approach coupled with anticipated reduction in production time. In the new model of production, pharmacists will be able to customize individual patients' specific medications or medication doses. This change, coupled with the capability to formulate multiple medications in a single preparation, could lead to improved adherence to therapy and will ease medication management. Furthermore, we anticipate that the amenability to personalized therapy will offer an effective management of acute and chronic conditions, which will decrease health care costs to society.

API production using continuous manufacturing process

The feasibility of continuous manufacturing in the pharmaceutical industry has previously been addressed.¹⁴ It was reported that the main barrier to the implementation of continuous manufacturing is a perceived limited ability to support multiple products owing to product-specific requirements. The diversity and complexity of the APIs further favor batch processing. In the batch processing, a relatively



Figure 1. Schematic overview of key steps in the proposed patient-specific and individualized drug manufacturing paradigm. The proposed new approach will entail synthesis and production of APIs at regional facilities for distribution to 503A or 503B compounding pharmacies for subsequent preparation of medicines (medications) for patients. Efficiencies of API production could be improved through adoption of the continuous manufacturing model. The proposed paradigm will ensure drug manufacturing at the point of care to circumvent current challenges of centralized mass drug production. Pharmaceutical compounding will be upgraded with 3D printing, artificial intelligence, and machine learning. The anticipated benefits of the new manufacturing paradigm are highlighted when compared with traditional large-scale manufacturing model. Abbreviations used: API, active pharmaceutical ingredient; 3D, 3-dimensional.

small number of temperature and pressure-controlled vessels are utilized for most of the reactions, and unit operations are used in the synthesis of APIs. Because this proposal assumes that API synthesis would still be performed on a large scale at centralized facilities, plant economics do not favor individualized continuous manufacturing. However, using FDA-registered chemical laboratories as small-scale, widely distributed API synthetic facilities, if correctly designed, could make this paradigm economically feasible. Continuous processes have already been developed for several drugs. The Medicines-For-All (M4ALL) effort has been a large step in this direction.^{15,16} The mission of M4ALL is to improve patient access to high-quality medications via decreased production costs, with efforts focused on reducing costs, increasing efficiencies, and providing technical innovation.¹⁷ Under a new paradigm, API manufacture could be scaled up or down based on product demand and use, keeping inventory control costs down and minimizing the need for extended storage. The new approach is amenable to Process Analytical Technology (PAT)/Quality by Design (QbD), which is already embraced by FDA and is well-integrated into the analysis of manufacturing processes by inline detectors. PAT utilizes critical process parameters to design, analyze, and control pharmaceutical manufacturing processes. QbD emphasizes product and process understanding, as well as control, based on science and quality risk management. The goal of QbD is to achieve meaningful quality specifications based on clinical performance and increase product development and manufacturing efficiencies.¹⁸ FDA supports the development and implementation of continuous manufacturing for drug substances and all finished dosage forms.¹⁹

Application of Big Data, artificial intelligence, and machine learning

Machine learning (ML) is a subfield of artificial intelligence (AI) that involves the use of automated algorithms to perform tasks that traditionally rely on human intelligence.²⁰ AI relies on and generates large volumes of diverse and dynamic data that can be processed and analyzed under Big Data. In drug manufacturing sector, these technologies will make production more efficient with faster output and less waste while reducing operating costs. AI has been applied to perform quality control, shorten design time, reduce materials waste,

improve production reuse, and perform predictive maintenance.⁹ Processes that usually involve human input or management of process data can be accomplished through Computer Numerical Control. Algorithms can be generated that ensure tasks are performed very precisely and analyze the processes to determine where and how they can be streamlined to meet the critical quality attributes of the product.

Big Data, AI, and ML will be very helpful in predictive forecasting of epidemic outbreaks or seasonal illnesses and give enough time in planning supply of all formulating materials and APIs at the correct location and time.²¹ Furthermore, Big Data can be used to guide treatment decisions by providing information about the cause of a disease, allowing the detection and diagnoses of diseases and helping to determine potential interventions to make in the future.²² AI and ML can be used together in mobile apps to help track patients' health parameters and help improve patients' adherence to medications.²³ Health-system pharmacists can use this collected information to determine changes to make to patients' dosing regimens or overall medication regimens to improve adherence and health outcomes. In addition, ML can process data far beyond the capacity of the human brain. Specialized and properly programmed computers can learn from data and then suggest treatment for a patient whose condition may be untreated or not adequately treated on his or her current therapy.²⁴

In pharmaceutical manufacturing, ML can increase efficiency, product yield and cost, and product quality. Altogether, these advanced technologies can improve the availability of necessary medications to patients and ensure that the correct interventions are made. The ability to customize medication could improve patients' adherence to their medication regimens. We envision that a patient health demographic card could be created for each area served by a specific pharmacy, which could be used to predict drug utilization by disease state prevalence. It is exciting to think what this could do for access to care and advanced pharmacy ambulatory care services in community settings. Data on quality processes and patient demand can be readily shared²⁵ among state boards of pharmacy throughout the country to meet regional needs.²⁶

Overall, the legal and ethical aspects of AI application in the upgraded pharmaceutical compounding must be satisfactorily fulfilled in accordance with laws and regulations that address confidentiality, privacy, and professional judgement in dealing with any aspect of patient sensitive information.

Conclusion

Current large-scale, centralized manufacturing practices necessitate drug products with numerous excipients to accommodate long shipping and storage times. This new paradigm describes an initial effort that, with the ingenuity of our scientists and engineers, can transform the way pharmaceuticals are produced, distributed, and ultimately used by patients. By transitioning to regional and local drug manufacturing and continuous processes, expensive unit operations and excipients can be eliminated, shelf-life requirements can be reduced, monitoring of manufacturing can be automated, and medications can be personalized. This paradigm can quickly be adapted to the manufacture of semisolid, liquid, and sterile products. All of this is expected to stimulate innovations that can employ high-skilled workers and create technologies that can be readily exported. No doubt that this will be challenging to accomplish, but it is time to go back to the future and produce medicines regionally and locally. Integrating new paradigms into current drug manufacturing practice will require collaboration with health-system pharmacists in understanding how medications should be dosed and which medications will need to be prioritized for production. Based on biofeedback data collected with the assistance of health-system pharmacists, manufacture of a patient's medication can readily be adjusted to meet the patient's current API and dosing requirements.

References

1. U.S. Food and Drug Administration. Drug shortage. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages>. Accessed April 26, 2022.
2. Office of the Center Director. Drug shortage management. Available at: <https://www.fda.gov/media/72447/download>. Accessed April 26, 2022.
3. Caulder CR, Mehta B, Bookstaver PB, Sims LD, Stevenson B. Impact of drug shortages on health system pharmacies in the Southeastern United States. *Hosp Pharm*. 2015;50(4):279–286.
4. Baumer AM, Clark AM, Witmer DR, Geize SB, Vermeulen LC, Deffenbaugh JH. National survey of the impact of drug shortages in acute care hospitals. *Am J Health Syst Pharm*. 2004;61(19):2015–2022.
5. U.S. Food and Drug Administration. Safeguarding pharmaceutical supply chains in a global economy. Available at: <https://www.fda.gov/news-events/congressional-testimony/safeguarding-pharmaceutical-supply-chains-global-economy-10302019>. Accessed April 26, 2022.
6. Bookwalter CM. Drug shortages amid the COVID-19 pandemic. US Pharmacist website. Available at: <https://www.uspharmacist.com/article/drug-shortages-amid-the-covid19-pandemic#:~:text=ABSTRACT%3A%20The%20uncertainty%20of%20coronavirus,disrupted%2C%20and%20drug%20shortages%20resulted>. Accessed April 26, 2022.
7. Food and Drug Administration. Strategic plan for preventing and mitigating drug shortages. Available at: <https://www.fda.gov/files/drugs/published/Strategic-Plan-for-Preventing-and-Mitigating-Drug-Shortages.pdf>. Accessed April 26, 2022.
8. Melnyk IA, Oyewumi MO. Integration of 3D printing technology in pharmaceutical compounding: progress, prospects, and challenges. *Annals of 3D Printed Medicine*. 2021;4:2666. <https://doi.org/10.1016/j.jstlm.2021.100035>.
9. Sartorius. The trending role of artificial intelligence in the pharmaceutical industry. Available at: <https://www.sartorius.com/en/knowledge/science-snippets/the-trending-role-of-artificial-intelligence-in-the-pharmaceutical-industry-599278#:~:text=The%20key%20benefit%20for%20pharma,well%20as%20more%20treatment%20choices>. Accessed April 26, 2022.
10. Cecchin E, Stocco G. Pharmacogenomics and personalized medicine. *Genes (Basel)*. 2020;11(6):679.
11. Hirshfield L, Giridhar A, Taylor LS, Harris MT, Reklaitis GV. Dropwise additive manufacturing of pharmaceutical products for solvent-based dosage forms. *J Pharm Sci*. 2014;103(2):496–506.
12. Aksu B, Paradkar A, de Matas M, Ozer O, Güneri T, York P. Quality by design approach: application of artificial intelligence techniques of tablets manufactured by direct compression. *AAPS PharmSciTech*. 2012;13(4):1138–1146.
13. İçten E, Giridhar A, Nagy ZK, Reklaitis GV. Drop-on-demand system for manufacturing of melt-based solid oral dosage: effect of critical process parameters on product quality. *AAPS PharmSciTech*. 2016;17(2):284–293.
14. Baxendale IR, Braatz RD, Hodnett BK, 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):781–791.
15. US. Food and Drug Administration. Modernizing the Way Drugs Are Made: A Transition to Continuous Manufacturing. Available at: <https://www.fda.gov/drugs/news-events-human-drugs/modernizing-way-drugs-are-made-transition-continuous-manufacturing>. Accessed April 26, 2022.
16. Souza JM, Galaverna R, Souza AAN, et al. Impact of continuous flow chemistry in the synthesis of natural products and active pharmaceutical ingredients. *An Acad Bras Cienc* 2018;90(1 suppl 2):1131–1174.
17. Virginia Commonwealth University. Medicines for all Institute. Available at: <https://medicines4all.vcu.edu/about/our-mission/>. Accessed July 27, 2022.
18. Yu LX, Amidon G, Khan MA, et al. Understanding pharmaceutical quality by design. *AAPS J*. 2014;16(4):771–783.
19. FDA. Quality considerations for continuous manufacturing. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-considerations-continuous-manufacturing>. Accessed April 26, 2022.
20. Sahu A, Mishra J, Kushwaha N. Artificial intelligence (AI) in drugs and pharmaceuticals [e-pub ahead of print]. *Comb Chem High Throughput Screen*. <https://doi.org/10.2174/1386207325666211207153943>. Accessed July 24, 2022.
21. Walch K. The increasing use of AI in the pharmaceutical industry. *Forbes*. Available at: <https://www.forbes.com/sites/cognitiveworld/2020/12/26/the-increasing-use-of-ai-in-the-pharmaceutical-industry/?sh=1607366d4c01>. Accessed April 26, 2022.
22. Hulsen T, Januar SS, Moody AR, et al. From big data to precision medicine. *Front Med (Lausanne)*. 2019;6:34. <https://doi.org/10.3389/fmed.2019.00034>.
23. Group S. A guide to AI in the pharmaceutical industry. Available at: <https://stefanini.com/en/trends/news/a-guide-to-ai-in-the-pharmaceutical-industry>. Accessed April 26, 2022.
24. Rajkomar A, Dean J, Kohane I. Machine learning in medicine. *N Engl J Med*. 2019;380(14):1347–1358.
25. National Association of Board of Pharmacy. Sharing compounding data, regulators strive to increase patient safety. Available at: <https://nabp.pharmacy/wp-content/uploads/2020/09/January-2020-Innovations.pdf>; April 26, 2022.
26. Food and Drug Administration. FDA in brief: FDA awards grant for information-sharing system and research of interstate distribution of compounded drugs, as part of agency's effort to help address risks with poor-quality compounded drugs. Available at: <https://www.fda.gov/news-events/fda-brief/fda-brief-fda-awards-grant-information-sharing-system-and-research-interstate-distribution>. Accessed April 26, 2022.

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