

“Pharmacy on Demand” To Revolutionize Drug Manufacturing and Care Delivery

A device, titled a “*pharmacy on demand*,” is capable of producing 1,000 distinct pharmaceutical drugs, with the device being tested on generic drugs to start, in a 24-hour period.¹ The *Massachusetts Institute of Technology* (MIT), in conjunction with the *Defense Advanced Research Projects Agency* (DARPA),² recently developed a device with the potential to revolutionize the pharmaceutical industry by condensing the time and steps required to manufacture drugs. The current prototype consists of reconfigurable components, e.g., reactors, precipitation tanks, and filtration and crystallization units, that are added or removed depending on the drug being created.³ The current iteration of the device, which is the size of a standard kitchen refrigerator, utilizes *continuous manufacturing techniques*, which eliminates many of the steps required to create pharmaceuticals under traditional *batch processing methods*.⁴ Recent developments suggest that this device may eventually be located in military battlefield hospitals, hard to reach areas, traditional hospitals, and pharmacies,⁵ as researchers have demonstrated the device’s current capabilities to produce pharmaceuticals commonly utilized in an inpatient setting, including Benadryl, Valium, Prozac, and a local anesthetic.⁶ This *Health Capital Topics* article will discuss the advent of this new technology, and briefly detail recent initiatives by private and public entities for expanding the use of continuous manufacturing techniques, such as the “*pharmacy on demand*,” as well as, the differences between *continuous* and *batch* manufacturing.

Until the introduction of *continuous manufacturing*, the only viable option for most pharmaceutical drug manufacturers was using the *batch processing method*,⁷ the production of pharmaceuticals in which “...*batches of chemicals are synthesized, then... cool[ed] down, then are synthesized again to create new compounds*.”⁸ Subsequently, the compounds created under batch processing must crystallize, filter, and dry, and then powder is added to create a tablet or capsule.⁹ Generally, the synthesis of chemicals and the subsequent creation into a tablet or capsule occur in separate facilities, and the entire process can take months to complete.¹⁰ In contrast, the *continuous manufacturing method* integrates the steps under batch manufacturing, and the processes “...*allow for raw materials to be input[ed] into the system and the finished product to be discharged from the system in a*

continuous fashion.”¹¹ In this type of pharmaceutical manufacturing process:

“...[A] *continuous-flow process enables integration of reaction, crystallization, purification, and formulation with advanced control and realtime monitoring capabilities, thus enabling the application of quality-by-design principles and miniaturization of the entire end-to-end manufacturing platform*.”¹²

The *Department of Defense* (DOD) has sought to advance continuous manufacturing in medicine in order to improve military access to pharmaceuticals commonly utilized in battlefield medicine. DARPA, in collaboration with MIT, assists in developing continuous manufacturing techniques with the goal of utilizing this technology in:

- (1) Field hospitals for military service personnel;
- (2) Remote areas during disease outbreaks; and,
- (3) Other strategic locations in the U.S.,¹³ which may include:
 - (a) Minimizing effects of drug shortages;
 - (b) Filling gaps in the orphan drug market;
 - (c) Assisting in the advancement of precision medicine by creating drugs tailored to specific biomarkers related to disease; and,
 - (d) Enhancing medication access to underserved areas, both nationally and internationally.¹⁴

To achieve these goals, DARPA’s continuous manufacturing programs, *Pharmacy on Demand* (PoD) and *Biologically-derived Medicines on Demand* (Bio-MOD), aim to create portable devices capable of producing multiple *U.S. Food and Drug Administration* (FDA)-approved drugs within a 24-hour timeframe.¹⁵ Current production rates of the PoD, within a 24 hour timeframe, are: 21,900 doses of Diphenhydramine; 2,596 doses of Lidocaine; 19,500 doses of Diazepam; 5,000 doses of Fluoxetine; 1,547 doses of Ibuprofen; 1,000,000 doses of Atropine; and, 1,200 doses of Doxycycline.¹⁶

During a recent St. Louis conference sponsored by the St. Louis Chapter of the American Society of Appraisers, Geoff Ling, M.D., Ph.D., FANA, FAAN (U.S. Army Col., Ret.), former director of the Biological

Technologies Office of DARPA, co-presented with HCC CEO Robert James Cimasi, MHA, ASA, FRICS, MCBA, CVA, CM&AA, on current and future technological developments in the healthcare industry, and discussed the benefits of this evolving technology in both military and civilian applications. Dr. Ling noted that PoDs may reduce the potential for “*drug shortages*” and “*orphan drugs*,” while also “*enhanc[ing] disaster responsiveness*” and providing “*cost and storage space savings*.”¹⁷

In addition to public sector investment in continuous manufacturing techniques for pharmaceuticals, many private sector companies in the pharmaceutical industry have begun to utilize this technique to produce their products. The effort to implement continuous manufacturing in the pharmaceutical industry began in 2007, when Novartis partnered with MIT for assistance in the company’s transition away from traditional batch processes.¹⁸ This effort has since expanded, with other companies contributing to the initiative of implementing continuous manufacturing techniques into company practice. On April 8, 2016, *Johnson & Johnson* (J&J) received approval from the FDA to switch their manufacturing process from *batch* to *continuous* in creating Prezista, a drug it produces for HIV-1 treatment.¹⁹ Within eight years, J&J hopes to manufacture 70% of its highest-volume products through a continuous manufacturing process.²⁰ Vertex shifted to continuous manufacturing in July 2015 for Orkambi, a drug it produces for cystic fibrosis.²¹ *GlaxoSmithKline* (GSK) invested over \$50 million in continuous manufacturing to manufacture amoxicillin for Augmentin, finding that the new technique “...allows medicine to be made cheaper, faster, and with a smaller impact on the environment.”²² Additionally, Pfizer entered into a collaborative arrangement with GSK in October 2015 to upgrade Pfizer’s previously-constructed continuous manufacturing system.²³

In April 2016, the FDA endorsed utilizing this new manufacturing process, finding that “...by eliminating breaks between steps and reducing opportunities for human errors during the stops and starts in the batch process, continuous manufacturing is more reliable — and safer” than traditional batch processing methods.²⁴ The FDA has cited certain advantages in continuous manufacturing that may lead to reduced healthcare costs, including: (1) shorter processing times by eliminating time-consuming steps in the manufacturing process; (2) smaller equipment and facilities to produce pharmaceuticals; and, (3) on-line monitoring for quality control.²⁵ In general, “[the] FDA will continue [its] efforts to encourage the advancement of continuous manufacturing as one of a variety of ways to enhance the quality of the medications used by the American public.”²⁶

However, implementing continuous manufacturing in the pharmaceutical industry may have certain drawbacks. Specifically, pharmaceutical companies have cited potential issues regarding intellectual

property rights and patient safety stemming from the utilization of portable pharmacies.²⁷ Drug manufacturers typically enjoy exclusive production rights to drugs they created for three to five years following development,²⁸ and portable pharmacies have the potential to intrude on those intellectual property rights by allowing the production of drugs outside of this exclusive right.²⁹ On the issue of patient safety, the FDA noted various concerns regarding the guarantee of patient safety with drugs produced from portable pharmacies, including: (1) the need to integrate analytical tools that implement feedback mechanisms based on data gathered by the device; (2) the defining of representative sampling to ensure drug quality over time; and, (3) an incomplete understanding of the continuous manufacturing process.³⁰ Since noting its concerns, the FDA has supported implementing continuous manufacturing by utilizing a science and risk-based approach,³¹ as well as establishing the *Emerging Technology Team* (ETT) to “...work[] directly with [the pharmaceutical] industry to help identify and resolve scientific issues for new technologies.”³²

While public sector agencies and private pharmaceutical companies have been at the forefront of developing and implementing continuous manufacturing, hospitals and pharmacies may also be significantly impacted by this new technology. For example, hospitals and pharmacies may implement portable pharmacies for emergency purposes;³³ just as emergency electrical generators alleviate issues caused by power outages, pharmacies or hospitals may use portable pharmacies to help alleviate drug shortages during disease outbreaks and high trauma volume.³⁴ Other potential benefits, such as avoiding the need for refrigeration, as well as avoiding dependency on single source manufacturers,³⁵ may help steer such organizations toward implementing this new technology.

Additionally, portable pharmacies may also impact the acceleration of the shift toward personalized medicine. The FDA noted, “[w]e are entering an era of precision medicine, when drugs must be made with unique features and provided more quickly to patients in need.”³⁶ Notable researchers believe that these objectives may be furthered by portable pharmacies.³⁷ Healthcare industry stakeholders may choose to follow the advancements of this evolving portable pharmacy technology, as it has the potential to create a disruption in the pharmaceutical industry, while also providing pharmacies and hospitals with additional avenues in implementing drug processing.

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