Leveraging Integrated Continuous Manufacturing to Address Critical Issues in the U.S. Military

Bayan Teisho Takizawa, MD, MBA; Stephen Christopher Born, PhD; Salvatore Mascia, PhD

ABSTRACT There is a tremendous opportunity to modernize the pharmaceutical manufacturing industry—relinquishing outdated machines that have been used for decades, and replacing them with state-of-the-art equipment that reflect more contemporary advanced technologies. This article describes how the implementation of continuous manufacturing, replacing outdated batch systems, can positively impact our health care sector. Important benefits will include the creation of advanced pharmaceutical manufacturing jobs in the United States, the establishment of capabilities and capacity to quickly produce drugs critical to U.S. citizens, the reduction of health care costs through more efficient manufacturing, and access to better quality drugs through more sophisticated and reliable production processes. Furthermore, the application of continuous manufacturing will enable the U.S. Government, in partnership with pharmaceutical companies, to address current issues such as drug shortages, national emergencies (eg, natural disasters or chemical, biological, radiological, or nuclear threats), the Strategic National Stockpile (ie, improving response time and reducing maintenance costs), and the delivery of critical drugs to distant geographies (eg, forward military bases). The article also provides a detailed example of a critical aspect of continuous manufacturing: the ability to overcome technical challenges encountered by batch technologies.

INTRODUCTION

Historical Background

The manufacturing of pharmaceuticals has lagged behind the research and development of new therapeutics. The same batch processes that were used over a century ago are still being used today, while other industries have moved forward with automated and continuous operations (eg, fine chemical, oil, gas, and food industries).[1] Current pharmaceutical manufacturing methodology consists of carrying out individual reactions in large batches (eg, vessels), and then running analytical tests on the end product to determine if it meets specifications. It is important to note that the large process volumes of these reactions require increased safety procedures/precautions, especially with raw materials or intermediates that are unstable or explosive in nature.

The products of these reactions are often transported to other sites, where they undergo additional reactions and further processing to form the final active pharmaceutical ingredient (API). The API itself is then shipped to another facility, where it is formulated and finally transformed into a tablet, pill, or other final dosage form (Fig. 1). The end result is a fragmented process with a very long lead time and very large plant footprint. It is not unusual for the production of a pharmaceutical product to take 200 to 300 days, from start to finish.[2]

In addition to being time-intensive, pharmaceutical production is also cost-inefficient ($65 B/year is wasted in inefficient pharmaceutical operations).[3] Quality is also a problem, as product recalls continue to plague the industry—over the last year (November 19, 2017 to November, 18, 2018) over 70 drugs were recalled, three blood pressure medications alone within a 2-week period.[4] This last fact is largely because the U.S. Food and Drug Administration (FDA) has been enforcing its regulations to improve quality standards during pharmaceutical production, and current manufacturers are finding it difficult to meet these standards. With all of these limitations associated with batch processes, it is clear that the pharmaceutical industry needs more advanced and reliable manufacturing capabilities.[5]

Furthermore, from a strategic perspective, rival countries of the United States have advanced their manufacturing capabilities, narrowing significantly the technological gap. A recent publication from the National Defense Strategy Commission, "Providing for the Common Defense," detailed this trend, including how China's investments in technology and manufacturing have resulted in considerable growth of their innovation and manufacturing sectors.[6] This expansion has not been mirrored by U.S. industry, resulting in a comparative disadvantage. Indeed, with the risk of trade wars escalating from mounting tensions among global superpowers, the United States is not well prepared, with its current manufacturing infrastructure, to ensure that all U.S. citizens will immediately receive the medications they need in the event of a major conflict. For example, close to 80% of the active and bulk pharmaceutical ingredients consumed by U.S. citizens is imported.[7] This overwhelming dependence on foreign suppliers that implement an outdated and substandard quality manufacturing method for life-saving products is particularly concerning.

CONTINUUS Pharmaceuticals, Inc., 25-R Olympia Avenue, Woburn MA 01801

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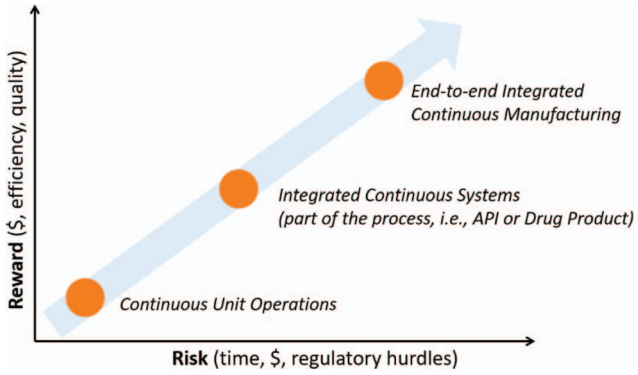

FIGURE 1. The current batch manufacturing paradigm is long, fragmented, and uncoordinated.

Objective

The authors believe that the United States should invest in drug manufacturing infrastructure to develop a "critical mass" of capability and capacity. This would ensure our ability to rapidly respond to potential crises that could affect our drug supply chain. In addition, this manufacturing base could address current issues, such as drug shortages that are affecting patient care. A recent survey of over 200 oncologists revealed that over 80% of them had to change the way they prescribe chemotherapy during the previous 6 months because of a shortage.[8] Thus, this is an issue that negatively impacts many U.S. citizens. Furthermore, the drugs in shortage are mainly small molecules (ie, structurally simple drugs that are chemically synthesized) that are off patent, low-margin, and often produced abroad by only a few and sometimes just a single manufacturer.[9]

From a military perspective, the proposed manufacturing capability will provide several key strategic advantages. First, continuous processes are much smaller than their corresponding batch units.[10] This will enable continuous manufacturing lines to be located closer to, or perhaps within military bases, providing soldiers better access to life-saving drugs. Second, because lead times with continuous processes are much shorter than with batch processes, the United States will be able to respond more rapidly and effectively to a biological, chemical, or nuclear attack that requires immediate medical care, both at home and abroad. Finally, the ability to produce medications within the United States will lessen its reliance on potentially rival nations, eliminating leverage they may have to compromise political, economical, and military options.

The proposed manufacturing facilities should be different from the stereotypical pharmaceutical plant. They should be automated to the extent possible. As U.S. wage rates are greater than those of competitor countries, it would be economically infeasible to implement a labor-intensive manufacturing line. They should be environmentally friendly. U.S. citizens do not want plants that discharge toxic solvents and wastes on U.S. soil. Furthermore, there are strict regulations that are enforced by agencies such as the Environmental Protection Agency. They should produce high-quality products. Regulators are demanding that manufacturers adhere to the high-quality standards set forth in the guidelines and regulations regarding drug production. Finally, they should be cost-effective. With the untenable growing cost of health care, the U.S. economy cannot support more expensive drugs. As described below, there is an opportunity to reduce the costs of these drugs.

This article will describe how innovative continuous manufacturing systems can help the United States achieve the aforementioned objectives. The authors will then provide a detailed example that highlights specific technical advantages when a strategically important drug is manufactured continuously.

PROPOSED SOLUTIONS

Current Continuous Manufacturing Efforts

The pharmaceutical industry is transitioning many of its traditional batch systems to continuous ones. In fact, several companies, such as Vertex Pharmaceuticals, Janssen, Eli Lilly and Company, and Pfizer, have received approvals for drugs with significant continuous manufacturing components.[11] However, efforts in this area have been very diverse, ranging significantly in their strategic objectives and extent. Figure 2 illustrates the risk and reward considerations for these different endeavors.

Continuous Unit Operations

Some pharmaceutical and biotech companies are inserting individual continuous unit operations in processes that are predominantly batch (ie, most of their other unit operations are batch in nature). For example, some companies are utilizing continuous perfusion reactors in the production of biological products (ie, structurally complex drugs that require living cells for production because chemical synthesis is not feasible or practical), such as Bayer (Kogenate), Janssen (Remicade), and Genzyme (Fabrazyme).[12] Perfusion bioreactors utilize living systems (eg, cells) to produce the biological compound of interest, just as batch bioreactors do; however, media and nutrients are continuously added, while the cellular products and additional byproducts and debris are continuously removed. In this way, the cells are always immersed in an environment that promotes the production of the biological product, allowing for continuous production. Many technologies and processes are currently being developed to increase the productivity of these systems.[13] Advantages of perfusion reactors include improved product quality, easier scalability, reduced capital and start-up costs, and reduced cost of contamination.[14] Examples of other continuous unit operations that are utilized in the pharma industry include chemical reactors and tableting machines. The Continuous Manufacturing and Crystallisation Consortium (CMAC) effort in the United Kingdom is an example of an academia-industry partner-

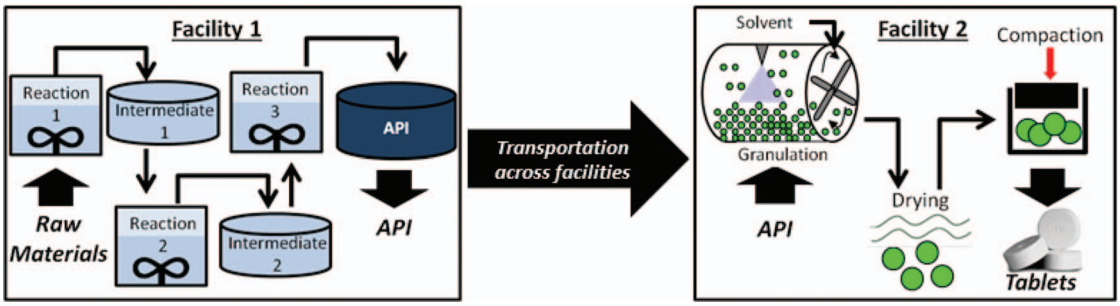

FIGURE 2. Continuous manufacturing efforts in the pharmaceutical industry vary significantly.

ship focused on developing continuous technologies, with an emphasis on crystallization processes. Centered at the University of Strathclyde, the collaboration engages in fundamental research and the development of solutions for specific industry problems. Many pharmaceutical companies are working with CMAC, including GlaxoSmithKline, AstraZeneca, Bayer, Eli Lilly, Novartis, Roche, and Takeda.

The application of single continuous unit operations is generally a less risky approach than more comprehensive and fully integrated continuous systems. However, the benefits are usually less substantial. The decision to implement this strategy may be based on the company's risk tolerance or specific challenges that require targeted solutions (eg, a certain chemical reaction performed in batch that poses a risk to operators). The authors believe that these efforts demonstrate the advantages of continuous unit operations, and provide entry points for more integrated, and beneficial, continuous solutions.

Integrated Continuous Systems (Part of the Process, ie, API or Drug Product)

Several companies are employing integrated continuous systems for parts of their manufacturing process. For example, Vertex Pharmaceuticals currently markets two cystic fibrosis drugs, Orkambi (lumacaftor/ivacaftor) and Symdeko (tezacaftor/ivacaftor and ivacaftor), which are produced continuously.[15] More specifically, Vertex employs a continuous technology called the ConsiGma system developed by GEA, in the production of these two drugs.[16] The ConsiGma platform integrates blending, wet and dry granulation, direct compression, drying (fluidized bed), milling, tableting, and coating steps into a single continuous system. In this way, API powder and the necessary excipients can be continuously fed into the ConsiGma unit, while finished coated tablets are continuously produced.

Another integrated continuous system was developed through a research collaboration called the Center for Structured Organic Particulate Systems (CSOPS), which included multiple academic and industry partners. The focus of this partnership was to develop an integrated downstream manufacturing platform for direct compression (from API to final tablet). The collaboration was successful, and through these efforts Johnson & Johnson was able to convert an existing batch process for the HIV medication Prezista to a continuous one, and obtain FDA approval.[17]

There are several advantages in employing integrated continuous solutions described above. They ensure better product quality, while reducing the cost and time associated with validation and scale-up efforts. In addition, their ability to quickly change production throughput allows manufacturers to quickly meet demand changes, while reducing inventory costs. However, one major challenge is that companies still need to source their APIs, which are likely produced by outdated batch processes. A solution to this problem is to adopt end-to-end integrated continuous manufacturing (ICM) systems, where API and DP are combined in the same production line.

End-to-End Integrated Continuous Systems

There are two end-to-end technologies that were recently developed at the Massachusetts Institute of Technology (MIT), though with different objectives. The first was funded by the Defense Advanced Research Projects Agency (DARPA), and has been commonly referred to as the "Pharmacy on Demand."[18,19] Through this project, a very small-scale, end-to-end manufacturing process for small-molecule drugs was created. This system consists of an upstream unit, where the reaction(s) take place, and a downstream unit, where the reaction products are crystallized, filtered, dried, and dissolved in a solution that can then be dosed to patients. Each unit is approximately the size of a household refrigerator, and modules within these 2 units can be interchanged and reconfigured to produce different drugs. Because these units are much smaller than conventional batch units, more extreme processing conditions can be used to achieve increased efficiencies. The throughput capacity of this system is considerable—thousands of doses can be produced each day. On-Demand Pharmaceuticals is currently advancing this platform technology toward commercialization.

The second end-to-end continuous manufacturing platform for small-molecule drugs developed at MIT was sponsored by a pharmaceutical partner, Novartis. As such, this project's objectives were more aligned with commercial manufacturing (ie, larger scale, traditional dosage forms). This $65 M joint research endeavor named the Novartis-MIT Center for Continuous Manufacturing, spanned 10 years, and included

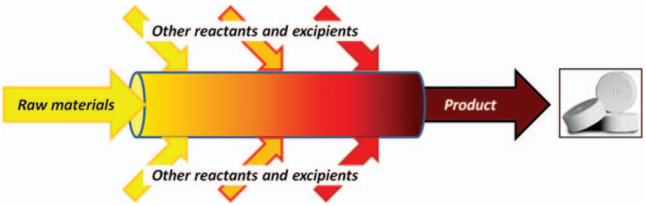

FIGURE 3. Concept of integrated continuous manufacturing of pharmaceuticals.

multiple disciplines, such as chemical engineering, mechanical engineering, and chemistry.[20] The collaboration was extremely successful, and led to the development of the first manufacturing prototype to produce finished drug tablets from raw chemical ingredients through a fully integrated, non-stop, end-to-end continuous process.[21] This platform, called ICM, was built on the concepts of continuous flow, end-to-end integration, systems approach, and integrated control strategy (Fig. 3). More specifically, this process proceeds from start to finish with no intermediate products that require isolation, storage, or shipping to another location (these steps are necessary with batch manufacturing). As a result, a commercial batch process that normally takes 200 days was reduced to just 2 days with ICM. The entire manufacturing train, which has approximately one-tenth the footprint of an equivalent batch line, was able to be located in a single room. CONTINUUS Pharmaceuticals is currently advancing this platform technology toward commercialization.

There are three major components that are critical to the ICM systems described above (for both end-to-end and partially integrated continuous lines):

Integration

The integrated unit operations operate as a single, seamless process that is not disrupted by the stops and starts that plague batch manufacturing. This includes more than just physically connecting the units; rather, it requires the methodical integration of the component technologies in such a way that the process is maintained in state of control, continuously producing product within specifications. This is done by rigorously identifying the critical process parameters (CPPs) (the operating parameters most critical to each step that affect the performance of downstream units and the quality of the intermediate and final products) for the entire process, implementing the appropriate monitors, and then linking these real-time measurements to automated control loops (feed forward and feed backward). For example, if temperature is identified as a CPP for a reactor in a manufacturing system, then it is important to monitor this parameter carefully. If it drifts beyond the "soft" limits (specifications that do not require diversion of process material to waste), the integrated control system may execute corrective steps to prevent further drift. Examples of such actions include: (1) reduced/increased heat to the reactor to correct the reaction temperature and (2) decreased/increased purification washes to a subsequent filtration unit to ensure that impurities are adequately purged. Because these algorithms are built into the control system, they will be executed more rapidly and reliably than any operator-driven intervention. An important feature of end-to-end lines is the system-wide approach that is utilized. Contrary to the fragmented batch system, where there is often a lack of communication between upstream manufacturers (ie, the manufacturers who produce API from raw materials) and downstream manufacturers (ie, the manufacturers who produce the final dosage forms from API), end-to-end systems are developed through a truly collaborative effort across the entire manufacturing line (ie, no more siloes). Another important feature is the elimination of work-in-process inventory. This offers drug manufacturers several advantages: (1) the degradation of intermediate products that are usually stored for long period of time will be virtually nonexistent, improving process/product quality; (2) the safety risk of unstable intermediates will be significantly reduced, as they will be immediately consumed by the next step; and (3) the economic risks and costs of holding inventory will be largely mitigated.

Modularity

It is critical that the unit operations that comprise an integrated continuous process can be utilized in a plug-and-play fashion to produce other drugs. More specifically, the unit operations of one manufacturing line must be flexible to be reconfigured into another line that produces another product, with minimal modification and changeover time. This will allow companies to practically and economically utilize the same unit operations to produce different drugs. The ICM process technologies are designed in this way—operating conditions are easily adjusted (eg, filter plates can be easily exchanged) to accommodate different compounds, and equipment are designed to be rapidly disassembled (ie, facilitated cleaning). In addition, it is important to deploy different unit operations, depending on the synthetic/purification steps required of the drug being produced. For example, some compounds can be produced through a Plug Flow Reactor, while others may require a chain of Continuously Stirred Tank Reactors.

Novel Continuous Unit Operations

In many cases, the application of novel continuous unit operations is necessary for integration to work. This is because most unit operations utilized in the pharmaceutical industry were made to operate in batch, and not in a continuous and integrated fashion. As a result of this limitation, some continuous manufacturing efforts utilize batch technologies in a semi-continuous or limited continuous fashion. Examples of novel continuous technologies include the continuous reaction module and continuous rotary filtration system initially developed at MIT through the DARPA and Novartis projects, respectively. These and other novel continuous technologies

not only facilitate integration, but they also enhance their performance.

Advantages of Continuous Technologies

There are many advantages associated with continuous manufacturing, in addition to those described above. As shown in Figure 2, the benefits of continuous manufacturing are generally greater with processes that contain more continuous components. Two of the major advantages, cost and quality, are described below.

Continuous processes can significantly reduce costs, as was shown with the ICM process developed at MIT.[22] Important contributors include: (1) Capital Expenditures—continuous equipment are smaller, and the total number of units can be reduced by eliminating corrective steps (eg, in the batch system, downstream drug formulators often have to correct for undesirable properties in the API, such as particle size); (2) Material Handling—with integrated systems, process material remains *in situ* (ie, within the process), and does not require personnel to transport it from one unit to the next; (3) Quality Assurance/Quality Control—integrated continuous processes are monitored and controlled real-time through integrated control systems that are fully automated, requiring fewer personnel; (4) Waste—continuous technologies generally will consume less raw material and be able to more effectively recycle solvent (eg, less entrained wasted in solvent recovery processes through improved yields); (5) Utilities—integrated continuous lines will require less energy to produce equivalent amounts of product (eg, reactors can be kept at their reaction temperatures for extended periods, not requiring energy-consuming heating and cooling cycles for each single batch); (6) Labor—integrated continuous lines are automated, requiring significantly less personnel; and (7) Raw Materials—continuous processes often provide higher yields (eg, better mass- and heat-transfer with smaller equipment) and require less solvent.

Continuous processes can improve quality, a view shared by the FDA.[23] This is because quality can be engineered into the process through a plant-wide Quality-by-Design (QbD) strategy. With QbD, a deep process understanding is attained to identify the CPPs that impact the Critical Material/Quality Attributes (important physicochemical properties of the process material that affect process performance and final product quality) of the intermediate and final products.[24] This is done through rigorous testing, both risk and statistically driven, and implementing the appropriate sensors (eg, thermocouples) and Process Analytical Technologies (spectroscopic-based instruments that provide real-time information about the process material, such as residual solvent) that monitor the process material throughout the manufacturing process. In this way, the entirety of the drug substance/product is being ensured for quality, removing the risk of sampling errors. An additional benefit of this instantaneous quality assurance approach is that it will enable real-time release-testing (ie, the ability to predict final product quality based on process performance, allowing manufacturers to release high quality product without additional testing) of pharmaceutical products, and consequently, on-demand manufacturing (ie, the ability to quickly respond to changes in demand).[25] Conversely, batch manufacturing utilizes an outdated testing protocol called Quality-by-Testing, whereby quality is ascertained through testing (eg, testing samples). This is done because of a lack of process understanding and the consequent need to verify that the intermediate/final product is within specification.

CASE STUDY

The Technical Benefits from Continuous Manufacturing

Oseltamivir, sold under the brand name Tamiflu, is an antiviral medication used to treat and prevent influenza A and influenza B (flu). It has been identified as a strategically important drug, and is currently stockpiled by the U.S. Government (for pandemic flu). It has an 8-month manufacturing lead time, and consequently, any response to address spikes in demand from seasonal or pandemic flu has been challenging.[26] This, in addition to its supply chain fragmentation has led to perennial shortages of this critical medication.[27]

This long lead time is attributed to the technically demanding manufacturing process of the drug substance. The sequence of steps starting from the advanced precursor epoxide 1 is time consuming and difficult (Fig. 4). The transformation of the key precursor epoxide 1 to the drug substance **7** essentially involves the conversion of an epoxide to a 1,2-diamino derivative, which utilizes hazardous azide reagents and produces unstable and toxic intermediates. More specifically, the *in situ* generation and use of hydrazoic acid (highly explosive and toxic) from sodium azide (explosive and toxic) in two of the steps requires significant measures to ensure safe processing.[28] This is attributed to the low boiling point (37°C) of hydrazoic acid, and the risk of it condensing in the pure state, which is extremely shock-sensitive (see temperatures in the first and third steps—60–65°C and 35°C, respectively). This condensation occurs on the lid and walls of the batch vessels used during manufacturing. Thus, to prevent catastrophic explosions, these vessels need to be: (1) engineered carefully, (2) monitored closely, and (3) safely contained.

Conversely, an example of the benefits of continuous manufacturing is the significant improvement in containment realized from using plug flow reactors. In a plug flow reactor, there is no headspace, and reactions can be operated at much higher temperatures and pressures (ie, to increase reaction rates, reducing manufacturing lead-times) in a safe, controlled manner. Moreover, reaction quenching and extraction can be readily performed using in-line membrane separators. Thus, the significant safety risks associated with processing hydrazoic acid can be largely mitigated—eliminating headspace will prevent the condensation of hydrazoic acid. Furthermore,

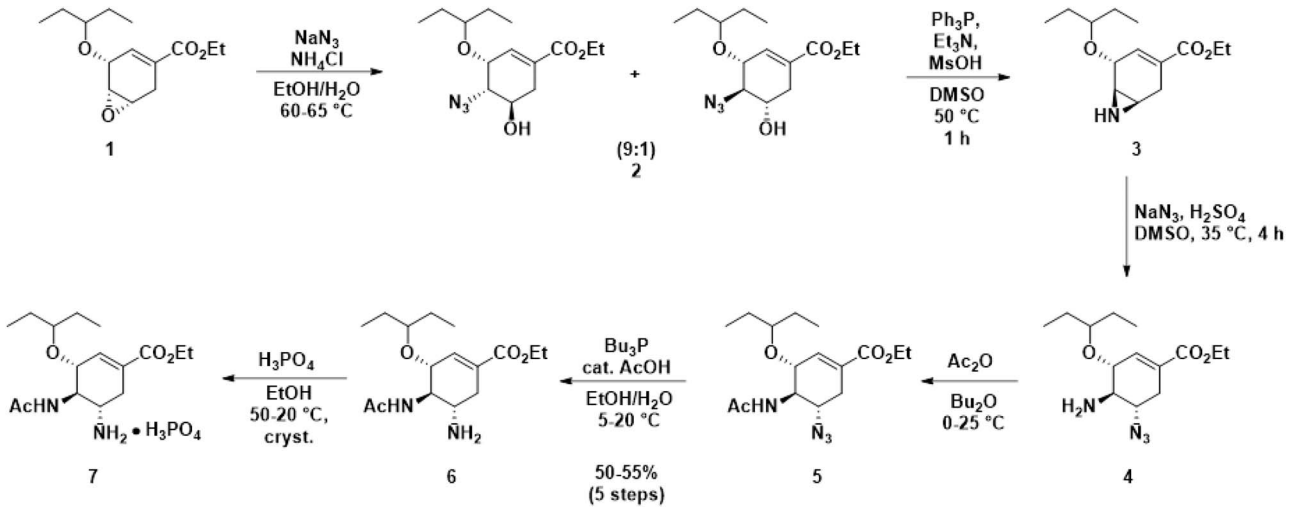

FIGURE 4. Current synthetic route of Oseltamivir Phosphate.

the hydrazoic acid that is formed in solution is done so in much smaller volumes (with ICM, production is possible 24 h/d), and is immediately incorporated in an addition reaction to produce the final product, Oseltamivir. Any excess hydrazoic acid is immediately quenched with base after this step. Thus, there is no accumulation of this highly explosive and toxic intermediate.

Continuous crystallization, filtration, and drying processes can be integrated with the proposed synthetic route to deliver the final API. Conditions can be optimized to obtain the desired particle size distribution through the manipulation of the nucleation rate, residence time, and temperature. Integrating multiple reactions, the crystallization, filtration, and drying steps dramatically reduces the processing time and can effectively eliminate the bottleneck in the current API manufacturing process. The authors believe that the manufacturing lead time can be decreased to days instead of months. Moreover, the described integrated continuous system will be safer and more economical.

CONCLUSION

This article illustrates how continuous manufacturing can provide significant advantages over batch technologies. As described above, there is a broad spectrum of efforts, ranging from the application of single continuous unit operations, to fully integrated end-to-end continuous lines. The different risk and benefit profiles of these approaches provides the pharmaceutical industry with numerous solutions to existing and future challenges. In addition, continuous manufacturing may help address the following critical issues:

(1) Drug shortages: At any given time, there are over 100 drugs on the FDA drug shortage list.[29] This affects patients and caregivers across the country, including those in military-based systems, such as the Veterans Administration hospitals. There are multiple reasons for these shortages, including manufacturing problems, limited profit margins (these drugs are mainly generic), supply chain disruptions (eg, shortage of the API), and plant shutdowns (eg, from a quality infraction). Continuous manufacturing, with its lower cost structure, shorter lead times, and improved quality assurance, may be used to produce these drugs, allowing patients to receive the medications they need.

(2) Quick response to disasters or threats: During national emergencies, such as natural disasters, disease outbreaks, or bioterrorist attacks, the ability to quickly produce the relevant medications/treatments at an appropriate scale can determine the severity of the event. Continuous manufacturing, with its significantly shortened lead time, is well positioned as a technology that can provide a robust response to such unfortunate events.

(3) Strategic National Stockpile: The Strategic National Stockpile, which protects U.S. citizens from national emergencies, such as natural disasters, disease outbreaks, and bioterrorist attacks, relies on batch manufacturing to stock its drug supplies. Continuous manufacturing, with its lower cost structure and shorter lead times, can reduce the cost of producing and maintaining these inventories (eg, shorter lead times reduce the amount of drug that needs to be stocked at any given time).

(4) Remote deployment: Current manufacturing lines are large and are unable to be mobilized to different areas. ICM lines, with smaller footprints, can be quickly mobilized to different regions of the world for strategic, military and/or humanitarian reasons. For example, they are small enough to be deployed at military bases, or even military ships, providing quick access to life-saving medications.

The establishment of in-country advanced manufacturing that will better position the United States to maintain a stable supply chain of life-saving medications is a critical imperative.

This endeavor will require the involvement of many parties, including the FDA and other relevant government agencies, such as the Biomedical Advanced Research and Development Authority and the Department of Defense, as well as private companies that have the technological expertise to drive this modernization effort. The authors believe the stakeholders are prepared for the mission, and the time is now!

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