

# Advanced Biopharmaceutical Manufacturing: An Evolution Underway



## Executive summary

The past decade has seen a significant shift in the nature of the products being manufactured and sold by the innovative biopharmaceutical (biopharma) industry. The global biopharmaceutical portfolio of today reflects increased therapeutic competition, a greater prevalence of large molecule drugs, expansion in the number of personalized or targeted products, and a rise of treatments for many orphan diseases. These trends have given rise to biopharmaceutical products with extremely limited production runs, highly specific manufacturing requirements, and genotype-specific products. This fundamental shift in the overall product mix and a focus on continuing to improve the efficiency and effectiveness of production is spurring an evolution in the technologies and processes needed to support advanced biopharmaceutical manufacturing.

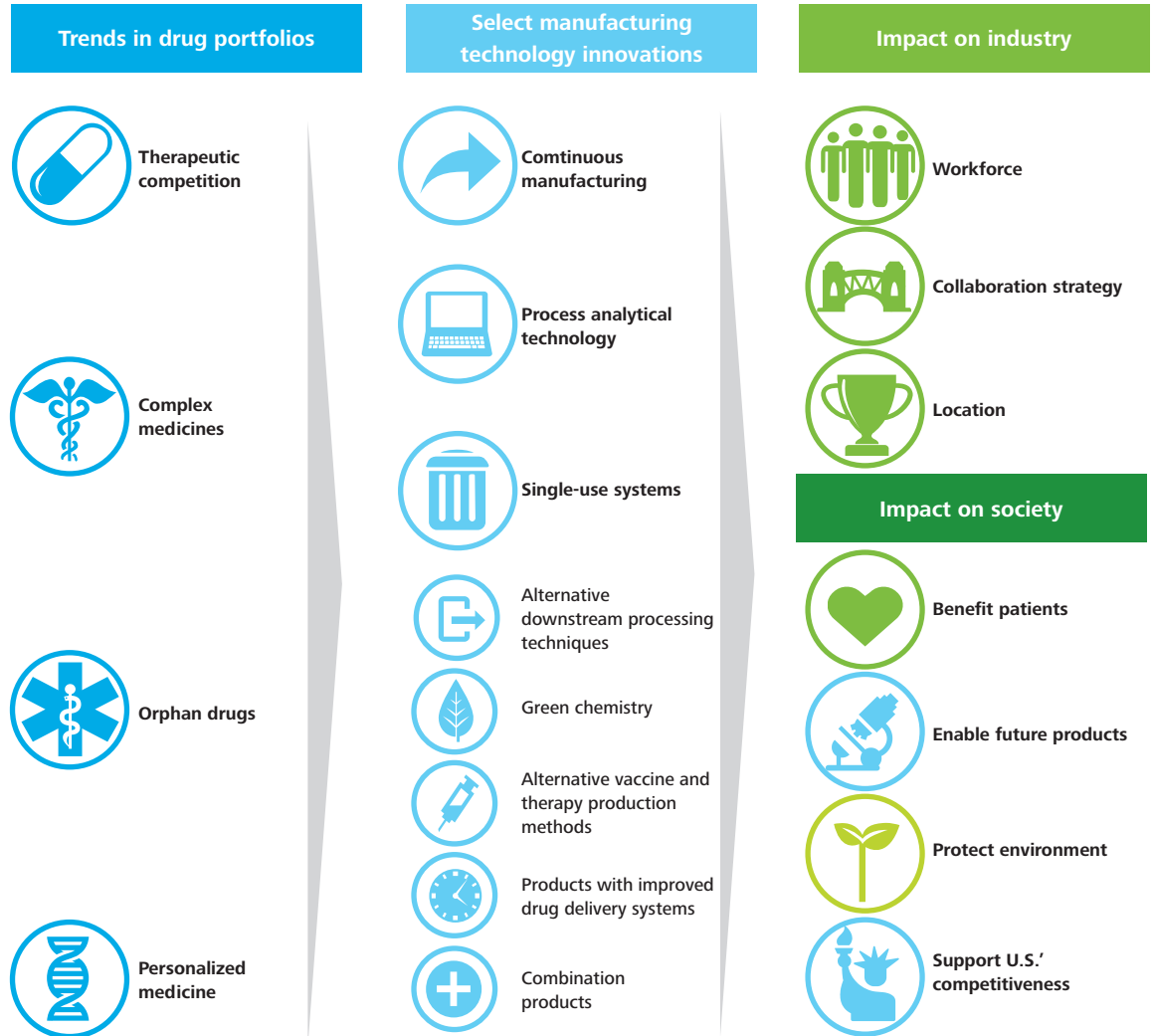
Innovation in manufacturing technology is helping to drive improved economics, flexibility and quality while potentially benefiting patients both directly and indirectly. Biopharmaceutical manufacturers are generally making investments in the following areas:

- Continuous manufacturing to improve scalability and facilitate time to market, while lowering capital and operating costs and enhancing quality
- New process analytical tools to improve process robustness, accelerate scale-up to commercial production and drive more efficient use of resources
- Single-use systems to increase flexibility and reduce production lead times, while lowering capital investment and energy requirements
- Alternative downstream processing techniques to improve yields while lowering costs, green chemistry to reduce waste, and new vaccine and therapy production methods to increase capacity, scalability, and flexibility.

Additionally, new types of products are coming to market that help increase the effectiveness of medicines and support patient compliance, such as products that reflect improvements in drug delivery systems and drug-device combination products. These products require advanced manufacturing techniques on the part of the biopharmaceutical company and its supply network, as the manufacturing process itself is becoming more central to the effectiveness of medicine.

The changes in biopharmaceutical portfolios and the rise of advanced manufacturing technologies have impacts both inside and outside of biopharma companies. First, they are driving biopharma companies to seek increasingly specialized workers who possess needed experience and skills. As a result, organizations are helping to design training programs at university biomanufacturing centers devoted to teaching relevant skills to students and employees. Second, the changes are causing biopharma companies to work collaboratively on manufacturing innovation through partnerships with academic institutions, diagnostics developers, production equipment manufacturers, and medical device manufacturers. Third, the new portfolios and technologies required are giving biopharma companies more reasons to consider location and ecosystem advantages in their strategic decisions around manufacturing. Finally, the rise of biopharmaceutical advanced manufacturing technologies is positively impacting society by benefiting patients, the environment, and the nation's standing as a leader in innovation — perhaps even enhancing overall U.S. competitiveness. [Figure 1]

Figure 1: Overview of select biopharmaceutical portfolio changes, manufacturing technology innovation, and potential impacts on industry and society



### Introduction to biopharmaceutical manufacturing

Biopharmaceutical manufacturing is generally characterized by the use of advanced technologies, harnessing of new scientific advances, and driven by a highly complex research and development (R&D) enterprise. The development of a novel compound typically requires large investments in time and capital to translate scientific discovery into new medicine and to build specialized manufacturing facilities and equipment, starting with the need to produce the initial supplies of an investigational compound for use in clinical trials (prior to scale up to full-scale production upon Food and Drug Administration (FDA) approval). Biopharmaceutical manufacturing aligns with research and development (R&D), and requires considerable scientific know-how and infrastructure. Likewise, an innovation ecosystem can serve as an overall enabler of manufacturing advances. For example, start-up hubs foster sharing of ideas and leading practices, while academic institutions often provide needed talent and resources. Advanced innovation ecosystems have often facilitated the connection between manufacturing and R&D for many biopharma companies.

Over the past decade, biopharma manufacturing has become a strategic driver with the ability to create and maintain market access through scalable and flexible operations, controlled costs, and high quality. While the biopharma industry has long focused on finding new ways to develop and launch new and innovative therapies in less time and at lower costs, in recent years the industry has increasingly turned its attention toward improvements in manufacturing technologies as well. Several of these

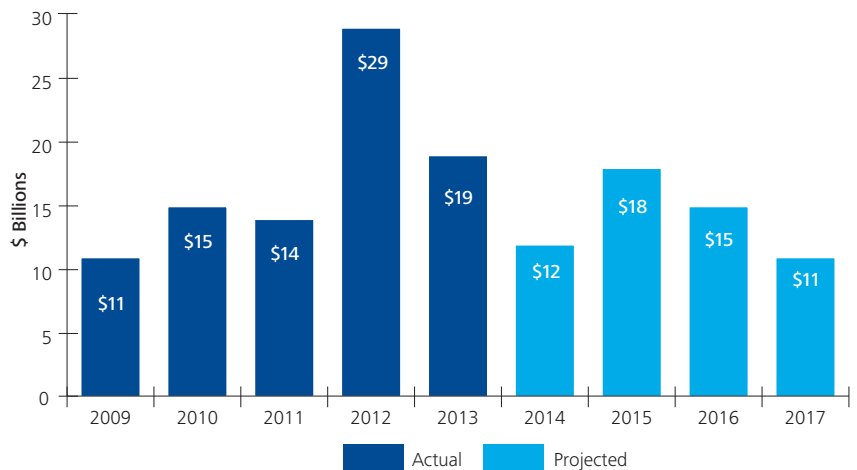
advances – in particular continuous manufacturing, process analytical technology, and single-use systems – mark a new stage in the industry’s development. These emerging technologies are generating further changes across the biopharmaceutical workforce and impacting manufacturers’ collaboration strategies and their choices of facility locations.

### Biopharmaceutical portfolio trends

Four overarching market (commercial) trends, all interrelated yet also distinctly separate, may have significant manufacturing implications and are driving the development and adoption of advanced manufacturing technologies:

- **Increase in therapeutic competition:** Although spend decreases due to drugs going off patent peaked in 2012 and 2013,<sup>1</sup> they are projected to continue to occur between 2015 and 2017<sup>2</sup> [Figure 2]. Furthermore, subsequent generation medicines that generally aim to outperform the efficacy, safety, disposition, or cost of earlier in-class innovator drugs, have helped to increase the level of competition amongst innovator manufacturers. Both of these industry developments are prompting biopharmaceutical companies to adopt a more strategic view of manufacturing and to seek further cost efficiencies in the manufacturing process. Additionally, the rise of subsequent generation medicines and generics, and soon, the introduction of biosimilars (subsequent entry or follow-on biologics) has raised the status of manufacturing as a key differentiator, as traditional biopharmaceutical innovator companies with strong manufacturing functions could become more adept at successfully targeting an innovator drug.

Figure 2: Estimated spend<sup>a</sup> reduction from loss of exclusivity (U.S.)

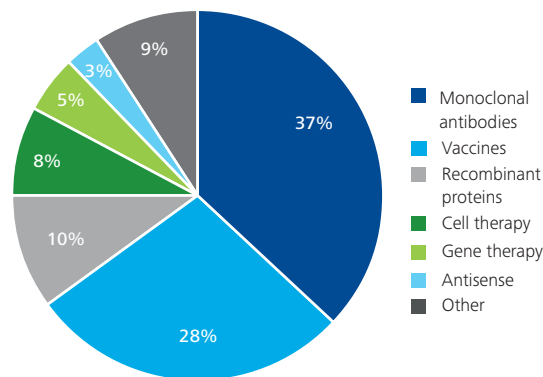


Source: IMS Institute for Healthcare Informatics, “Medicare Use and Staffing Cost of Healthcare,” April 2014, 32. IMS Institute for Healthcare Informatics, “The Global Use of Medicines: Outlook through 2017.” November 2013, 24; Deloitte Consulting LLP Analysis.

<sup>a</sup>Spend on patented drugs within the U.S. healthcare system

- **Greater prevalence of complex medicines:** The FDA has approved at least 10 large molecules (biologics) in each of the past five years<sup>3</sup>. Furthermore, over 900 biologics were in development as of February 2013,<sup>4</sup> suggesting that there will be increased need for commercial production of biologics in the coming years [Figure 3]. Biologic medicines such as vaccines are complex molecules made by or from living cells and are often infused or injected. As such, they require highly specialized manufacturing, special storage and handling, and a tightly controlled, high quality manufacturing and distribution network to ensure safety and effectiveness.

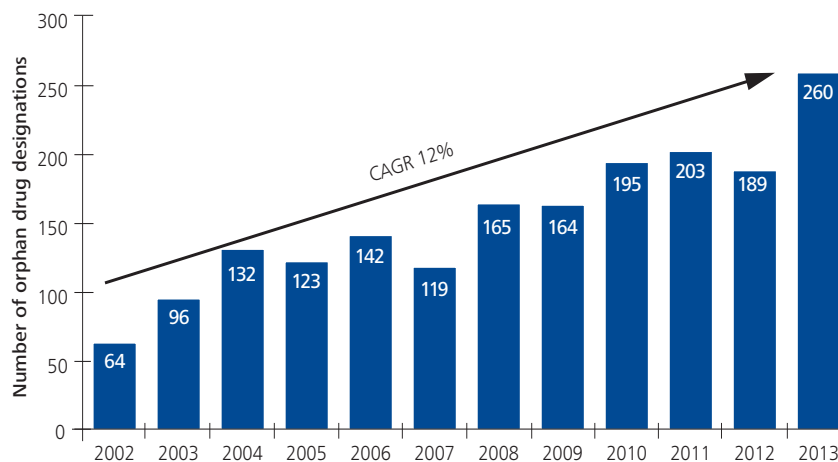
**Figure 3: Biologic drugs in development by category, 2013**



Source: Pharmaceutical Research and Manufacturers of America, "Medicines in Development: Biologics," 2013

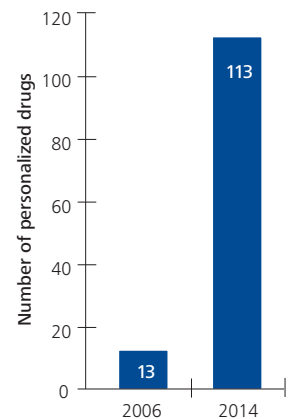
- **Growth of orphan drugs:** The number of FDA designations of orphan drugs (drugs aimed at diseases with patient populations of under 200,000) has increased steadily over the past decade, from 131 in 2004 to over 250 in 2013 [Figure 4];<sup>5</sup> this indicates that manufacturers are increasingly focusing on some of the most complex diseases for which there are few or no effective treatments. New treatments for these diseases are characterized by small volume products that must reach patients who are often widely geographically dispersed. Furthermore, in 2013, the FDA approved 17 orphan drugs, the most it has approved in any single year.<sup>6</sup> Global orphan drug spend in 2013 was 41 percent higher than it was five years prior, and it is expected to almost double by 2020.<sup>7</sup> Orphan drugs have created the need for manufacturing flexibility (the ability to use equipment, labor, and supplies for more than one product) because of their relatively small volumes. Additionally, orphan drugs have put pressure on manufacturing volume management, as production processes can often yield larger batches than the required volumes.
- **Emergence of personalized medicine:** The number of personalized drugs, products that target a specific population of patients, has risen in recent years, increasing from just a handful in 2006 to over 100 in 2013 [Figure 5].<sup>8</sup> Furthermore, the FDA has stated that about 80 percent of its approximately 50 designated "breakthrough" therapies (drugs that either treat a serious condition or demonstrate significant improvement on an existing drug) involve targeted

**Figure 4: Number of orphan drug designations (U.S.)**



Source: Evaluate-Pharma, "Orphan Drug Report 2014," October 2014, 15

**Figure 5: Number of personalized drugs on market (U.S.)**



Source: Personalized Medicine Coalition, "The Case for Personalized Medicine," First and Fourth Editions, 2006 and 2014

therapies.<sup>9</sup> However, these targeted products may only represent an early stage of personalized medicine. Over time, as patient-level personalized medicines are introduced, manufacturing and product supply complexity will likely increase, as each unit should have a unique “SKU.” Furthermore, they may require patient-specific genetic inputs (e.g., blood), and thus manufacturing processes will need to accommodate small or scale batch specificity. Finally, as personalized drugs generally are accompanied by companion diagnostics, manufacturers are increasingly developing diagnostic manufacturing expertise or partnering with diagnostics companies.

These drug portfolio trends have contributed to an increase in the number and complexity of products being manufactured and sold. First, they have resulted in greater product variety and increased occurrences of small-volume runs, which require frequent changeovers and may necessitate equipment reconfigurations and updates. Second, the complex nature of in-market and pipeline medicines have increased demand for materials that need to be kept sterile and are often manufactured into mechanisms such as syringes and other devices. Additionally, the new medicines have increased the need for more complex manufacturing processes, more advanced equipment, and cold chain or controlled storage. Overall, these drug portfolio trends indicate that mastering manufacturing excellence through innovation is a strategic driver in creating flexibility with uncompromised quality, while creating operating efficiencies that can help reduce costs.

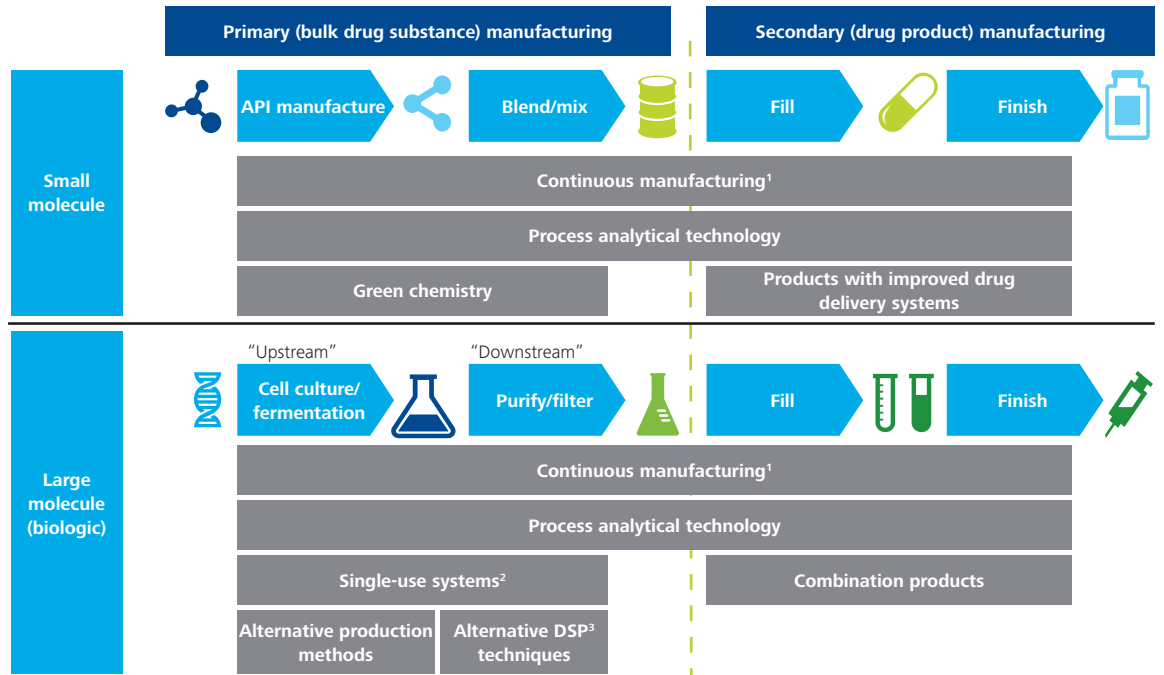
### **Manufacturing technology innovation**

In the world of discovering and developing medicines, chemistry and biology are at the heart of manufacturing. Manufacturing advances in the biopharmaceutical industry contribute increasingly sophisticated enhancements to these fundamental processes. Research that yields a promising new molecule, for example, may require new applications of chemistry and biology to synthesize the molecule, and new or improved facilities and equipment to transform living material into a medicine.

Most small molecule drugs are manufactured through organic or inorganic chemical synthesis, whereas large molecule (biologic) drugs are manufactured through live cellular expressions. To produce small molecule drugs, the manufacturer combines specific chemical ingredients to make the drug substance or active pharmaceutical ingredient (API). The resulting small molecule drug has a relatively simple, well-defined chemical structure. Accordingly, a manufacturer can analyze the finished product and ensure that the product meets the approved quality specifications. To produce large molecule (biologic) drugs, however, the manufacturer uses live microbial cells (plant or animal sourced cells) to synthesize biological drug substance or API. The resulting biologic is a very large, complex molecule (often 200 to 1,000 times as large as a small molecule and usually comprised of proteins). Given the size and complexity of large molecules (biologics), manufacturers often face substantial manufacturing challenges. Therefore, manufacturers generally place a high emphasis on ways to improve the consistency and predictability of processes over time to ensure product quality; hence the industry saying “The product is the process.”<sup>10</sup>

Manufacturing technology innovation contributes increasingly sophisticated enhancements to chemical and biological processes. The innovation spans primary and secondary manufacturing, the two general steps in the drug production process. While some advances relate solely to small molecule or large molecule (biologic) production – primary or secondary manufacturing – biopharmaceutical manufacturers are innovating throughout the entire process from raw material to finished drug products. These advances – continuous manufacturing, process analytical technology, single-use systems, and other new technologies – have enabled manufacturing flexibility and scalability while improving quality and throughput and controlling costs [Figure 6]. Regarding biologic drug production specifically, through the use of single-use bioreactors, disposable plastic containers, continuous purification processing, and real-time quality analysis, companies are developing the next generation of biomanufacturing.

Figure 6: Overview of manufacturing processes and technology innovation



<sup>1</sup> Investments in continuous manufacturing have mainly involved primary manufacturing. However, investments in continuous manufacturing are also involving secondary manufacturing.

<sup>2</sup> Single-use systems have primarily been used for upstream processing. However, companies have begun to experiment with it for downstream processing as well.

<sup>3</sup> Downstream processing.

### Continuous manufacturing

*Continuous manufacturing can improve scalability and facilitate time to market, and help lower capital and operating costs and enhance quality.*

Some biopharmaceutical companies have begun utilizing continuous manufacturing as an alternative to batch manufacturing in various parts of the production process. In a continuous manufacturing system, raw materials are continuously fed into a process train while finished product materials are continuously removed at the other end [Figure 7]. Although the amount of material being processed at any given instance may be relatively small, the process may be run over a long period of time to generate required quantities of finished product. In essence, a continuous manufacturing system is an end-to-end automated assembly line; other industries such as food products and specialty chemicals have used continuous manufacturing for years.

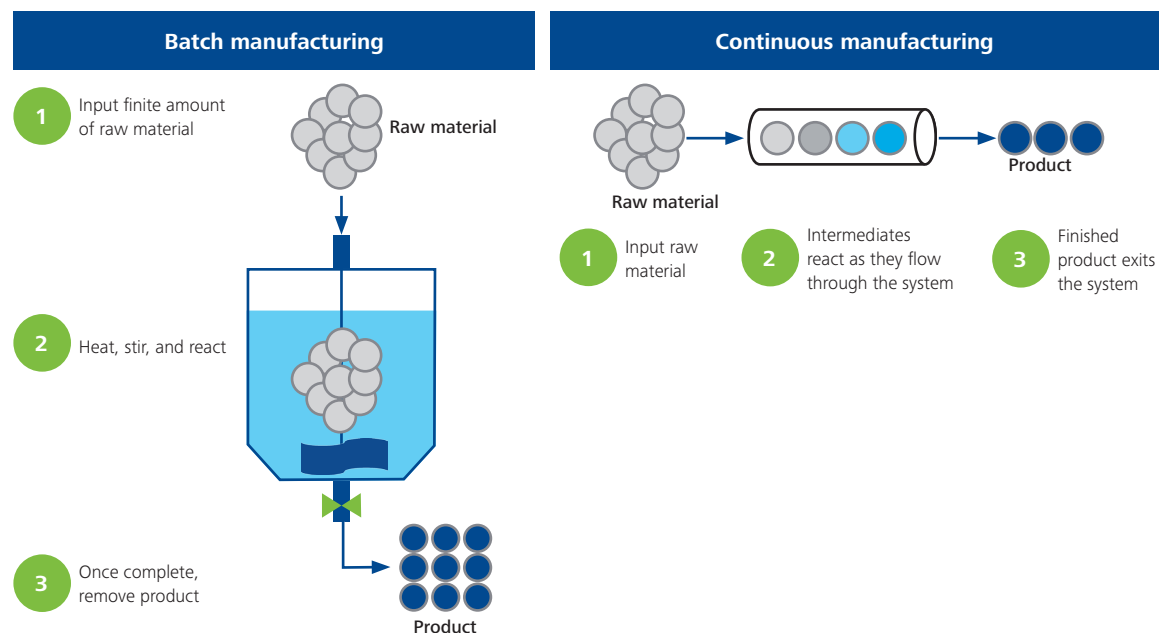
Continuous manufacturing is being explored for both small molecule and large molecule (biologic) drugs, and both primary and secondary manufacturing.

Some companies have developed continuous technology for certain parts of their manufacturing process, but few, if any, have announced the use of a fully continuous bioprocessing system in commercial production. For example, companies such as Bayer and Genzyme have been using continuous perfusion technology for large molecules (biologics) in the initial phase (fermentation) of upstream processing for the past two decades and at least 12 products manufactured

with perfusion or similar technologies are on the market.<sup>11</sup> In continuous perfusion, manufacturers constantly supply cell lines (microbial or mammalian) with fresh growth medium and continuously harvest culture media for prolonged time periods (e.g., months). In September 2014, Genzyme filed a patent application that integrates upstream and downstream continuous bioprocessing.<sup>12</sup> For small molecules, Pfizer has deployed continuous tablet coating on some products to streamline a common bottleneck step. Pfizer is also exploring continuous crystallization technology to get more consistent physical properties of APIs.<sup>13</sup>

The potential advantages of continuous manufacturing are impressive. Continuous systems are much smaller in size than batch systems, thus they can produce as much or as little product as needed.<sup>14</sup> Furthermore, smaller vessel sizes require fewer and less complex setup cycles. As a result, limited scale-up from clinical manufacturing is necessary (i.e., resulting in commercial scale production during clinical development), which implies faster time to market and could reduce the potential for drug shortages.<sup>15</sup> Continuous manufacturing technologies can drive operating efficiencies like increased capacity and material utilization, reduced offline quality control and analysis, and less maintenance, energy use, and product loss, resulting in operating cost savings of 9-44 percent.<sup>16</sup> Capital expenditures for continuous systems have been estimated to be 20-76 percent lower than for batch systems,<sup>17</sup> as their footprints have been estimated to be potentially 40-90 percent smaller.<sup>18</sup>

Figure 7: Batch versus continuous manufacturing



Source: US FDA, Deloitte Consulting LLP analysis

Continuous manufacturing can decrease production times, especially for small molecule products. For large molecules (biologics), it can improve quality by constantly maintaining media nutrients and avoiding lags that reduce cell viability.<sup>19</sup> Finally, smaller reactor sizes offer greater flexibility – a five-liter continuous bioreactor can produce as much as a 5,000-liter traditional bioreactor.<sup>20</sup>

Continuous manufacturing does, however, have its own challenges. First, continuous manufacturing technology development is in direct competition with long-term investments in existing batch manufacturing sites, so the industry has been slow to move away from batch manufacturing. Second, continuous manufacturing poses a challenge of how to define a batch for the purposes of quality control, for example, in cases of product recall. As a result, continuous manufacturing requires new methods of measuring quality and gathering metrics. Third, continuous manufacturing may not be ideal for low-volume, high-value products, as the amount of product lost in starting up, reaching steady state, and change overs or shut downs can have significant value.<sup>21</sup> Finally, continuous manufacturing requires process developers to view manufacturing plants holistically rather than as a string of unit operations,<sup>22</sup> and have an integrated multi-disciplinary approach across technical and manufacturing areas and engineering disciplines.

The FDA views continuous manufacturing as consistent with the FDA's quality by design efforts, as it has resulted in a more modern manufacturing approach, enables quality to be directly built into process design, and has the potential to improve assurance of quality and consistency of drugs.<sup>23</sup> Likewise, the FDA has encouraged the biopharma industry to approach manufacturing process development for new products using the continuous manufacturing paradigm. The FDA has been collaborating with the industry through regular attendance at workshops and conferences (such as the International Symposium on Continuous Manufacturing at the Massachusetts Institute of Technology (MIT) in May 2014) and has been supporting research and collaboration with a number of academic institutions.<sup>24</sup>

### Process analytical technology

*New process analytical tools can help improve process robustness, accelerate scale-up to commercial production and drive more efficient use of resources.*

The FDA defines process analytical technology (PAT) as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes."<sup>25</sup> PAT primarily comes in the form of knowledge bases that contain information collected from experiments over

time, multivariate programs that compare quality and performance attributes, and equipment that measures biological, chemical and physical attributes, as well as univariate factors. PAT equipment can make measurements at-line (when a sample is removed from the manufacturing process permanently), on-line (when a sample is removed from the process and then returned), or in-line (when a sample is not removed at all).<sup>26</sup> In manufacturing with PAT, continuous monitoring determines if the process is operating as expected and allows correction of errors at the time of their occurrence.

The overarching goal of PAT is ensuring final product quality. PAT is based on the FDA's perspective that "quality cannot be tested into products; it should be built-in or should be by design."<sup>27</sup> PAT is well aligned with the R&D process, as companies can begin using it in clinical manufacturing and then continue to use it during scale-up in an effort to ensure consistent quality and reduce time to market. Additionally, PAT enables real-time release testing and parametric batch release (release of product based on information collected during the production process), which can further increase quality assurance.<sup>28</sup> From a cost perspective, the improvement from PAT can help drive reduced costs in the form of fewer recalls and less scrap inventory. In addition, PAT enables more efficient use of equipment and manufacturing capacity, as well as the ability to adapt to variability in raw materials; again potentially, reducing overall costs. Finally, the advancement of continuous manufacturing is largely connected to PAT. As continuous processes by definition do not have stoppages or support traditional product quality testing, PAT addresses the need to monitor product continuously, raise any specification exceptions immediately, or adjust the process through advanced process controls based on predictive manufacturing process models (i.e., model predictive process controls).

In 2004, the FDA began encouraging the use of PAT to improve the efficiency and effectiveness of manufacturing process design and control, as well as to facilitate innovation in manufacturing.<sup>29</sup> PAT was already in use by industries such as petrochemical and consumer products at the time. By the late 2000s, many biopharmaceutical companies began to adopt the technology on certain products or in parts of the manufacturing process. For example, Novartis has used PAT tools and statistical analysis to improve its understanding of antibody yield. Novartis recorded process variables throughout the upstream process, and then analyzed "golden" batches (batches with high antibody yields) to define reference trajectories for the variables.<sup>30</sup> However, when taking entire product portfolios and end-to-end manufacturing processes into consideration, PAT adoption is still in the growth stage.



PAT has at least two major challenges to adoption: investment in skill development and initial setup. Manufacturing functions may need to train personnel on the analytical and process control skills required for proper PAT use.<sup>31</sup> Furthermore, employees may need to become increasingly comfortable thinking “end to end” instead of in functional silos and working with an evolving set of process protocols.<sup>32</sup> Regarding initial set up, PAT requires a high degree of process understanding and knowledge of critical parameters, especially during the initial set-up and operation of instruments.

### Single-use systems

*Single-use systems can help increase flexibility, reduce production lead times, and lower capital investment and energy requirements.*

Over the past few years, more large molecule (biologic) manufacturers have been adopting single-use technology, generally disposable plastic supplies, in lieu of stainless steel equipment throughout the production process. For example, manufacturers have significantly increased their use of disposable media bags and bioreactors in the upstream activities of cell culture and media and buffer mixing.<sup>33</sup> Furthermore, over the past year or two, some have been starting to employ single-use technology in downstream processes such as filtration and chromatography and in ancillary equipment such as connectors, tubing and sensors.<sup>34</sup> In fact, today, companies can implement single-use technology at nearly every step of the production process (and can use it to enhance some aspects of continuous bioprocessing).<sup>35</sup> They just need a business case to determine extent of implementation.<sup>36</sup>

Single-use systems can offer several benefits to biopharmaceutical manufacturers. They can modularize manufacturing and create flexibility in using the same floor space to manufacture different types of low volume products. They can significantly reduce the potential of cross-contamination,<sup>37</sup> facilitating rapid changeovers and multiple product production. In 2013, Catalent, a contract manufacturer, opened a 100,000 square foot clinical scale manufacturing facility based on single-use technology for both of these reasons.<sup>38</sup> Single-use systems are generally much smaller in size than traditional systems; thus, they generally require less capital investment and can help simplify qualification and validation procedures,<sup>39</sup> potentially shortening the time to commission a new facility. They require less sterilization, maintenance, chemicals, clean steam, and energy,<sup>40</sup> reducing overall operating costs and environmental impact.

Of course, as with most new technologies, single-use systems do pose some challenges. Most disposable systems have a maximum production scale of 2,000 liters, while many commercial production facilities have a scale of

10,000-25,000 liters. Due to this size difference, many manufacturers have found that using disposable equipment for high-volume runs is not cost-effective.<sup>41</sup> The second challenge is related to the actual equipment. Using plastic disposables inherently outsources part of the validation process to the supplier. Different suppliers use different materials in their disposables, and thus manufacturers run risks of extractables or leachables if they switch suppliers or if suppliers change their products.<sup>42</sup> Finally, standard recycling practices are not yet prevalent in the industry. As a result, some of the environmental benefits of single-use systems are countered by the need to use incineration or landfill to dispose of contaminated plastic. However, many suppliers are currently developing recycling programs to address this issue.<sup>43</sup>

### Other areas of technology innovation

While the technologies discussed above are among some of the most significant ones emerging today, technologies in several other areas are also evolving:

- **Alternative techniques in downstream bioprocessing:** *Alternative downstream processing techniques can lead to increased output while lowering costs.* Downstream processing does not currently have significant economies of scale – producing additional product requires more buffer, tanks, filters, and chromatography. As a result, companies see it as an area ripe for technological advances.<sup>44</sup> Protein A alternatives are one area of current innovation. Protein A is an immunoglobulin binding molecule and a tool commonly used in the detection and purification of antibodies.<sup>45</sup> Protein A chromatography is expensive due to high materials cost (\$12,000-15,000 per liter) and the recycling, cleaning, and validation that it requires.<sup>46</sup> Many suppliers have alternatives to Protein A in development and scientists have found that alternative resins may offer better alkali resistance, higher binding capacity, and improved reusability.<sup>47</sup> However, this technology is still in its infancy; in a survey by BioPlan Associates, 30% of companies stated they had investigated alternatives and 7% had implemented them.<sup>48</sup> As the large molecule (biologic) market continues to grow, this may change. A related area of innovation is membrane filtration technology. Membrane filtration can replace separation methods such as rotary vacuum filters or centrifugation that are used in harvesting. Such an alternative can improve product yields and reduce maintenance and labor.<sup>49</sup> In the survey by BioPlan Associates, 49% of companies stated consideration of the change to membrane filtration.
- **Green chemistry:** *Green chemistry can reduce waste and environmental effects.* Green chemistry, as described by the American Chemical Society Green Chemistry Institute (ACS GCI), involves “finding creative

and innovative ways to reduce waste, conserve energy, and discover replacements for hazardous substances.” In recent years, biopharmaceutical companies have collaborated through the ACS GCI Pharmaceutical Roundtable to develop innovative green chemistry tools and education resources.<sup>50</sup> Internally, companies such as Pfizer have increased the connection between R&D and manufacturing to find green solutions.<sup>51</sup> Companies are employing green chemistry through at least two routes. One route includes replacing many solvents with safer alternatives and designing processes that have lower carbon footprints and reduce emissions and energy use.<sup>52</sup> Bristol-Myers Squibb was one of the pioneers in this area, having a green chemistry scorecard in place in 2002.<sup>53</sup> Another route is biocatalysis, using natural or genetically engineered enzymes that are renewable and biodegradable in lieu of synthetic chemicals. In 2012, Merck received FDA approval to apply a biocatalytic process in the manufacture of an API for a diabetes drug; the new process reduced waste by 19% and earned the company the 2010 Presidential Green Chemistry Award.<sup>54</sup>

### Products with improved drug delivery systems

In addition to using new technologies to make existing products, companies are also using innovation to make new products with enhanced drug-delivery mechanisms.

- *Bilayer tablets* — tablets with two layers of medicine. While these tablets first entered the market years ago, advanced forms are now growing in use. Bilayer tablets administer doses of different APIs, control delivery rates and separate incompatible APIs.<sup>†</sup> However, they require specialized tablet presses that often run slowly and require careful die table cleaning and dust extraction.<sup>‡</sup> They also require additional R&D to prevent cross-contamination or delamination.<sup>‡‡</sup>
- *Oral thin films* — thin films covered in drug molecules. Widely used for over-the-counter medicines, their use is now spreading to prescription medicines. Oral thin films release medication directly into circulation. However, they require specialized equipment such as rollers and dryers, and additional R&D to determine appropriate polymers, optimal temperature, and thickness.<sup>‡‡‡</sup>
- *Products in development* — Needle coated tablets deliver large molecules to the lining of the stomach for better absorption.<sup>‡‡‡‡</sup> Implantable or injectable thin films deliver drugs over an extended period of time by limiting hydrolysis.<sup>‡‡‡‡‡</sup> These products require new types of equipment and an adjusted fill/finish process.

- **Alternative methods of vaccine and therapy production: Use of mammalian cell-based or other alternative methods of production can increase capacity, scalability, and flexibility.** Recently, some manufacturers have attempted to change their methods of growing viruses in vaccine production in order to increase production capacity, scalability, or flexibility. Companies have produced vaccines for many diseases using animal cell cultures since the 1950s.<sup>55</sup> Vaccines produced using mammalian cells have advantages over

vaccines produced using chicken eggs, such as: (1) lack of dependence on egg supply, allowing production at any time (2) standardized and reproducible process, resulting in greater consistency among batches (3) storable culture materials, enabling quicker scale-up (4) ability to easily incorporate virus strain changes, facilitating adjustment for new viruses and (5) lack of a need to adapt the virus seed strains to make them suitable for growth, expediting production.<sup>56</sup> Novartis has begun to use cultured mammalian cells in lieu of fertilized chicken eggs in the production of flu vaccines. In 2012, the FDA approved Novartis’ vaccine, the first U.S. flu vaccine that uses animal cells instead of chicken eggs.<sup>57</sup> In 2014, the FDA approved Novartis’ North Carolina facility for production of the vaccine.<sup>58</sup> (Novartis has since announced the sale of its influenza vaccines business, including the facility.)<sup>59</sup> The facility has capability to produce 200 million doses (enough to cover nearly two-thirds of the U.S. population) within six months and started shipping product in September 2014.<sup>60</sup>

Similarly, some manufacturers changed their methods of growing antibodies in therapy production. In 2014, Amgen, which uses mammalian cells to produce some of its drugs, assigned several staff to help create antibody production lines using Chinese Hamster Ovary (CHO) cells for Mapp Biopharmaceutical’s ZMapp™ antibody therapy in development to treat Ebola.<sup>61</sup> Mapp Biopharmaceutical has developed the therapy; to date, Reynolds American has manufactured the antibodies for the drug by growing them in tobacco cells.<sup>62</sup> Amgen supported the work of the Bill and Melinda Gates Foundation, the World Health Organization, and other organizations, to help create antibody production lines using CHO cells to enable production on a larger scale.<sup>63</sup>

- **Drug-device combination products: Combination products can enhance the effectiveness of medicines and often support patient compliance.** While medical device companies have had manufacturing responsibility for some drug-device combination products such as drug eluting stents, transdermal patches, and inhalers, biopharmaceutical companies are assuming a larger role in production for other combination products such as pre-filled syringes (PFS), needle-free devices, and sensor embedded tablets. Recent innovations in PFS include improved plastic material and lubrication to reduce leachables and extractables,<sup>64</sup> as well as online vacuum filling and stoppering;<sup>65</sup> these innovations require manufacturing collaboration between biopharma and device companies. Advances in needle-free systems such as tubeless pumps and instruments that deliver drug product into skin tissue may require biopharma

companies to develop new fill capabilities. Sensor-embedded tablets, such as those in development by Proteus, a company whose corporate investors include Novartis, Otsuka, and Medtronic,<sup>66</sup> may require biopharma manufacturers to adjust their traditional stamping processes. Combination products have a number of benefits to patients: they provide controlled or monitored release, enable drug delivery to a targeted area (increasing efficacy and decreasing side effects), and increase patient compliance<sup>67</sup> (sometimes doing so by shifting care from in-patient to out-patient).

### Impacts of manufacturing advances on the U.S. biopharmaceutical industry

The changes in drug portfolios and advances in manufacturing technologies are influencing biopharmaceutical manufacturers' workforce, collaboration, and location strategies. While at first glance, the major developments in the U.S. biopharma industry over the past few years may be seen as intense merger and acquisition activity, demand growth from healthcare reform, and the rise of specialty pharmacies, the manufacturing landscape has also changed and will likely continue to do so.

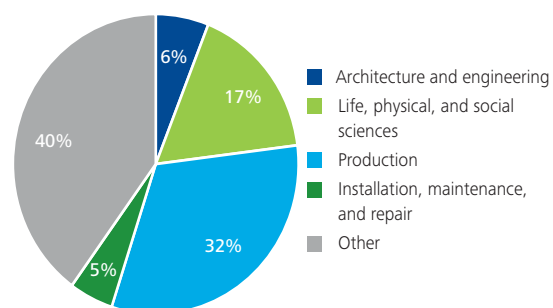
### Driving workforce development

The required capabilities for biopharmaceutical manufacturing workers have increased. Education levels required for manufacturing are rising, in part, due to the growth in large molecule (biologic) manufacturing. Whereas a high school diploma used to be sufficient to secure some biopharmaceutical manufacturing positions, now an associate's degree, or a high school diploma plus some relevant studies or certification, is generally the standard for a biopharma manufacturing operator. Areas of study have diversified, as basic knowledge of finance, enterprise resource planning, and the overall supply chain are viewed as beneficial to understanding can be applied to advances such as continuous manufacturing and single-use systems. And, while process analytical technology is generally driven by employees with specialized process control and statistical skills, some statistical knowledge by other manufacturing workers can be useful. From a scientific education perspective, the lines between disciplines have blurred and multi-skilled scientists provide a unique value to biopharma companies. In spite of the changing educational requirements, vocational training programs and high quality hands-on training continue to be important.

Today's typical biopharmaceutical manufacturing function does more than supply product. Technology advances have helped manufacturing evolve into a strategic function, and as a result, the emphasis on creating leaders within the manufacturing function has increased. Companies have realized that their manufacturing leaders should focus on the "end to end" global supply chain, as opposed to operating in silos (e.g. production, engineering, quality) and effectively managing their own separate businesses, as they may have done previously. Finally, although the need for close interaction between R&D and manufacturing is not new, the new complexities in manufacturing have elevated that need even further – manufacturing employees with some R&D perspective are becoming increasingly valuable. In terms of workforce numbers, between 2011 and 2013 the U.S. biopharmaceutical manufacturing workforce increased four percent overall to more than 277,000 employees, with the core production-related occupations increasing eight percent to more than 166,000 employees [Figures 8 and 9].<sup>b,68</sup>

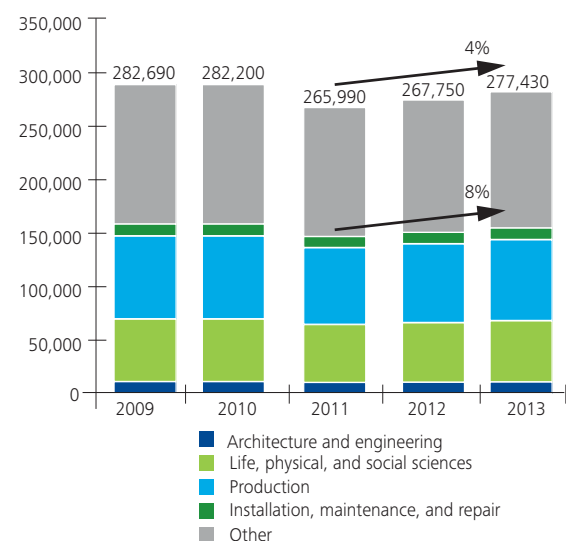
These amplified education and vocational workforce requirements are prompting biopharmaceutical companies to nurture the development of the biomanufacturing talent pool. In 2013, Worcester Polytechnic Institute (WPI) in partnership with AbbVie, Biogen Idec, the Massachusetts Life Science Center (quasi-government agency) and other companies, opened the Biomanufacturing Education & Training Center (BETC). The BETC is a fully functional biopharmaceutical manufacturing pilot plant that provides hands-on training and educational opportunities for students and employees. WPI operates the BETC, but industry partners develop curricula and mentor students.<sup>69</sup> North Carolina has a similar center, the Golden LEAF Biomanufacturing Training & Education Center (BTEC), which North Carolina State University and other North Carolina organizations formed in 2007.<sup>70</sup> The BTEC has an

Figure 8: U.S. Biopharma manufacturing employment, 2013



Source: U.S. Bureau of Labor Statistics

Figure 9: U.S. Biopharma manufacturing employment, 2009-2013



Source: U.S. Bureau of Labor Statistics

<sup>b</sup>Bureau of Labor Statistics; Deloitte Consulting LLP Analysis. Note: Total employment in the biopharmaceutical sector has been estimated to be considerably larger. A recent estimate that more completely captures jobs in R&D, distribution, and corporate headquarters put the total number of direct jobs in the industry at about 810,000 in 2011.<sup>68</sup>

advisory board comprised of leaders from several biopharma companies.<sup>71</sup> As of the 2013-2014 academic year, the BTEC had grown enrollment by over 350 percent since its launch.<sup>72</sup>

Developments are also occurring at the community college and high school levels. The NC BioNetwork Capstone Center, operated by a number of schools with biomanufacturing associate's degree programs, held its first job fair in 2012.<sup>73</sup> While company-sponsored science, technology engineering, and math (STEM) programs at the high school level have existed for decades, companies have enhanced the real-life aspect of programs in recent years.

#### **Increasing collaboration**

The advanced manufacturing race is encouraging biopharmaceutical companies to more closely collaborate with academic engineering institutions, similar to how they have collaborated with academic medical institutions for years. Continuous manufacturing has been the focal point of at least two of these partnerships. In 2012, Novartis and MIT, after five years and \$40 million of Novartis funding,<sup>74</sup> completed an experimental continuous production line in a 24x8-foot clear plastic case.<sup>75</sup> The line can turn raw materials into tablets to treat high blood pressure and heart failure in 47 hours; the process would have taken 300 hours with batch manufacturing.<sup>76</sup> Novartis has since moved the technology to its headquarters for further study, while MIT researchers are continuing to research continuous reactions and tools for other drugs.<sup>77</sup> In 2013, Janssen, the National Science Foundation, Rutgers University, Purdue University, New Jersey Institute of Technology, and other organizations completed a full-scale continuous tableting line.<sup>78</sup> Janssen developed a continuous tableting line for an HIV infection drug at its Puerto Rico plant based on the model, and the university researchers are continuing to work with at least ten industry partners to further advance continuous manufacturing technology.<sup>79</sup>

Biopharmaceutical manufacturers are also forming new partnerships with equipment manufacturers as a result of the emerging manufacturing technologies. In 2013, Pfizer, GEA Pharma Systems, and G-CON Manufacturing (a Texas-based portable equipment manufacturer) collaborated to develop portable manufacturing facilities known as PODs. PODs can be quickly deployed and moved, enabling small-lot, quick scale-up production and manufacture in regions without significant capital investment.<sup>80</sup> In 2014, Pfizer partnered with California-based Jacobs Engineering (a technical production and service provider) to develop a modular process system known as a rapid deployment module (RDM). RDMs integrate modular equipment, automated control systems and single-use technology;<sup>81</sup> like PODs, they can help facilitate global growth.

#### **Leveraging location and ecosystem advantages**

The portfolio changes and manufacturing advances give biopharmaceutical companies several reasons to consider locating their production facilities in the U.S. and other developed markets where strong biopharma ecosystems exist. Specifically, locating within the U.S. has several potential advantages. First, companies can meet the elevated need for communication and collaboration between R&D and manufacturing by locating within the U.S., as many companies already have major R&D facilities in the U.S. Furthermore, overall, the U.S. has the world's largest R&D output (defined as medical publications, industrial R&D spending, medical science patents, and biopharmaceutical-related venture capital deals),<sup>82</sup> largely due to its R&D ecosystem and infrastructure, which makes it an advantageous place to locate manufacturing. Second, the U.S. (especially the states of North Carolina, Massachusetts, and California) has a deep talent pool bolstered by programs dedicated to biopharmaceutical workforce development, which are helping manufacturing job candidates achieve the enhanced capabilities required today. Third, the drug portfolio changes, specifically the decreased size of production runs and higher number of products, may favor locating in the U.S. to help relieve the time and cost of international technology transfers for low-volume products. Finally, while large molecule (biologic), personalized and orphan drug demand will likely grow in emerging markets in the coming years, the high concentration of large molecules (biologics) and complex medicine demand in the U.S. may still make the U.S. an advantageous location from a streamlined supply chain perspective.

#### **Impacts of manufacturing advances on society**

The potential impacts of advanced manufacturing technologies do not stop at biopharmaceutical manufacturers' talent, collaboration, and location strategies. Instead, they extend throughout the industry and society, and could benefit the patients of today and tomorrow, the environment, and help boost U.S.' global competitiveness.

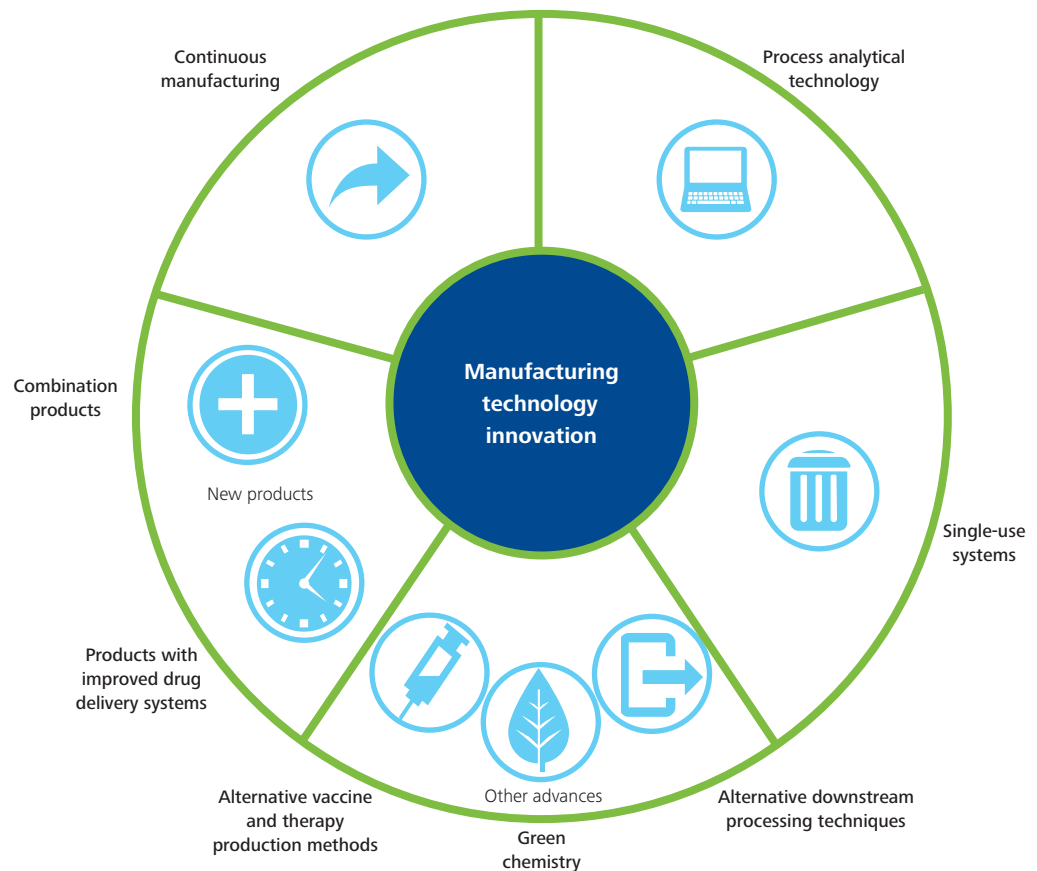
At the most basic level, patients are the ultimate beneficiaries of manufacturing innovation. Most of the new technologies help to drive faster scale-up, potentially expediting the entry of new life-saving products to market, and can elevate manufacturing yields. Meanwhile, new combination products and products with advanced drug delivery features could help improve prescription adherence, potentially resulting in more effective treatment for patients. The advanced technologies being implemented generally yield fewer quality issues and/or have a positive economic impact, thereby potentially enabling more resources to be spent on R&D and the drugs of the future.

Secondary to patients, yet still important to society overall, are the environment and U.S.' global competitiveness. The emerging technologies often use less energy and raw materials and create less waste, potentially decreasing effects on the environment and reducing manufacturers' carbon footprints. Meanwhile, these advances could help reinforce the U.S.' position as a leader in innovation, as manufacturing advances and R&D go hand in hand. As a result, the advanced manufacturing technologies could help bolster the U.S.' status as an attractive location for biopharmaceutical manufacturing.

### Conclusion

The need for high quality and readily available complex medicines is fueling innovation in biopharmaceutical manufacturing technologies, [Figure 10] which in turn, is driving changes to the industry overall and providing potential benefits to society. From an industry perspective, the advances have motivated biopharma manufacturers to take strategic actions around the manufacturing workforce, collaborations, and location. From a societal standpoint, they have generated benefits to patients, and also may have positive effects on the environment and the U.S.' global competitiveness. Manufacturing technology innovation is interrelated with R&D discoveries, as advances in one area necessitate advances in the other. As biopharmaceutical portfolios continue to evolve, and manufacturing technologies continue to advance in coming years, the biopharmaceutical industry and the U.S. overall are poised to embrace the opportunity.

Figure 10: Key areas of manufacturing technology innovation



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