Biopharmaceutical Manufacturing in the U.S.:

Making Cutting-Edge Medicines Today and Leading the Way on Medicines of Tomorrow

Prepared for the Pharmaceutical Research and Manufacturers of America (PhRMA)

March 2019

TECONOMY PARTNERS LLC

Introduction

This chart pack provides facts and figures about the significant economic contributions of the biopharmaceutical manufacturing industry, its role in the overall biopharmaceutical innovation ecosystem and its standing as a global leader. It also examines the complex and evolving technologies and processes involved in biopharmaceutical manufacturing, along with the extensive and strict regulatory standards it must meet to a degree unmatched in other manufacturing industries.

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U.S. Advanced Manufacturing Matters

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Sustaining the competitiveness of manufacturing in the U.S. matters to U.S. economic growth and prosperity

"Manufacturing serves critical public purposes that make it indispensable to the U.S. economy. It remains a source of high-wage jobs for virtually all types of workers … Manufacturing is the major source of commercial innovation in the United States … It accounts for the majority of U.S. foreign trade."

Brookings Institution, "Why Does Manufacturing Matter? Which Manufacturing Matters?" February 2012

"[A]n economy that lacks an infrastructure for advanced process engineering and manufacturing will lose its ability to innovate. … [T]he capacity to undertake advanced process engineering and complex manufacturing is as important to continued innovation as are strong universities and a robust venture capital industry."

Pisano, GP and Shih, WC, "Restoring American Competitiveness," Harvard Business Review, 2009.

The National Science and Technology Council identified biopharmaceuticals as a priority advanced manufacturing area, in addition to other technology areas such as

- advanced materials
- nanomanufacturing
- flexible electronics
- and additive manufacturing, among others.

--Subcommittee for Advanced Manufacturing of the National Science and Technology Council, "Advanced Manufacturing: A Snapshot of Priority Technology Areas Across the Federal Government," April 2016

U.S. Biopharmaceutical Manufacturing Matters

Biopharmaceutical manufacturing stands out among U.S. manufacturing industries for its economic contributions, innovation-led development and specialized nature

Significant Economic Contributions:

U.S. biopharmaceutical manufacturing industry is an economic powerhouse that drives economic growth, investment and quality jobs.

Innovation-led Manufacturing:

Complex medicines are both developed and made by U.S. biopharmaceutical manufacturing industry

Specialized, Highly Regulated Manufacturing Processes:

As scientific breakthroughs lead to the discovery of new medicines, it also increases the need for more complex manufacturing processes, conducted under strict requirements mandated by the U.S. Food and Drug Administration

A Global Leader, but Many Challenges Beset Sector

U.S. biopharmaceutical manufacturing leads the world, but faces numerous regulatory, reimbursement and competitive challenges

Significant Economic Contributions of Biopharmaceutical Manufacturing Industry

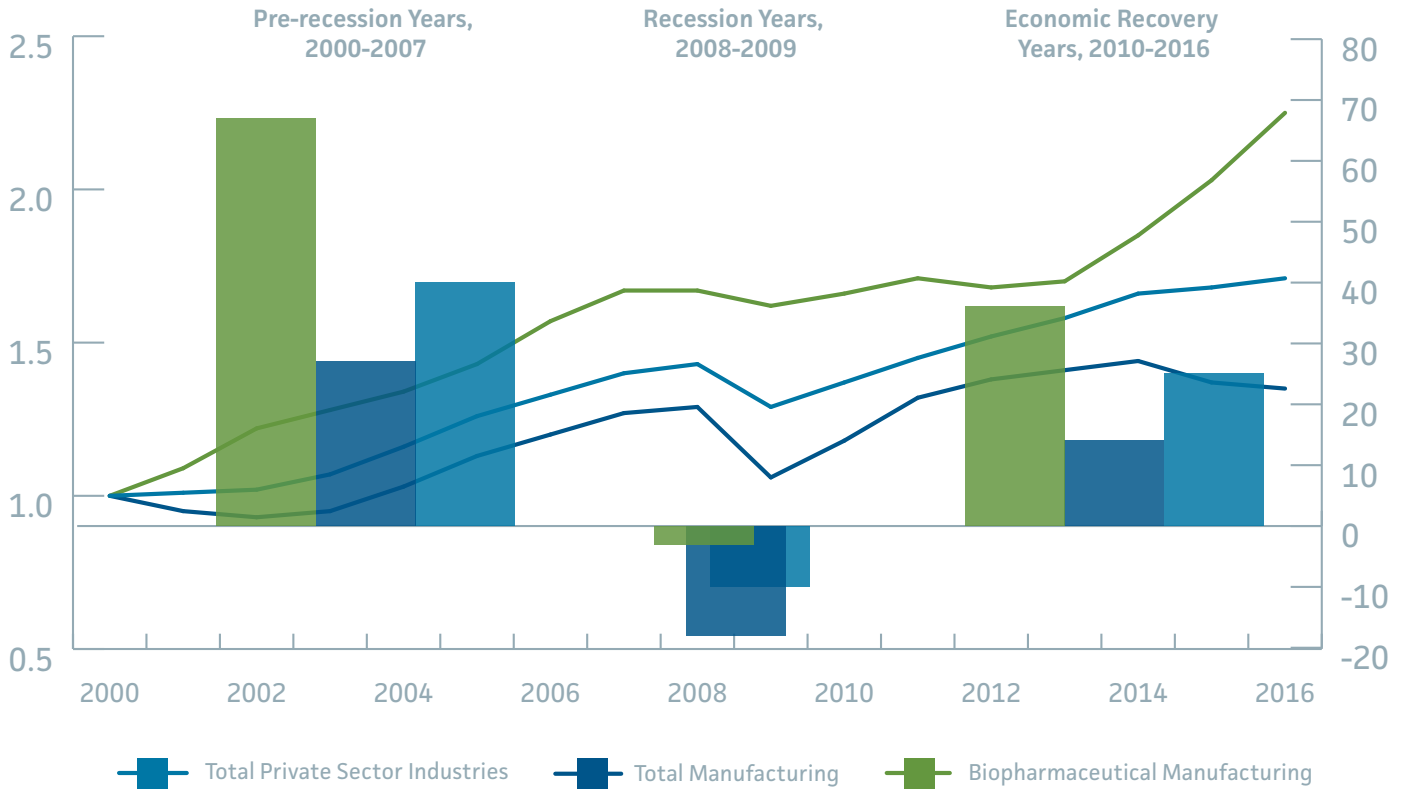
Significant Economic Contributions of Biopharmaceutical Manufacturing Industry

The biopharmaceutical manufacturing industry stands out as a dynamic industry providing the following benefits:

- Results in strong gains in economic output while overall manufacturing lags
- Operates at high level of productivity
- Provides high wages in production-related jobs
- Supports broad range of production occupations
- Provides outsized and growing levels of investments in building new and retrofitting existing facilities to manufacture medicines of the future
- Generates high level of exports
- Results in significant economic spillovers across construction and other related manufacturing industries

Generates Consistently Strong Gains in Economic Output

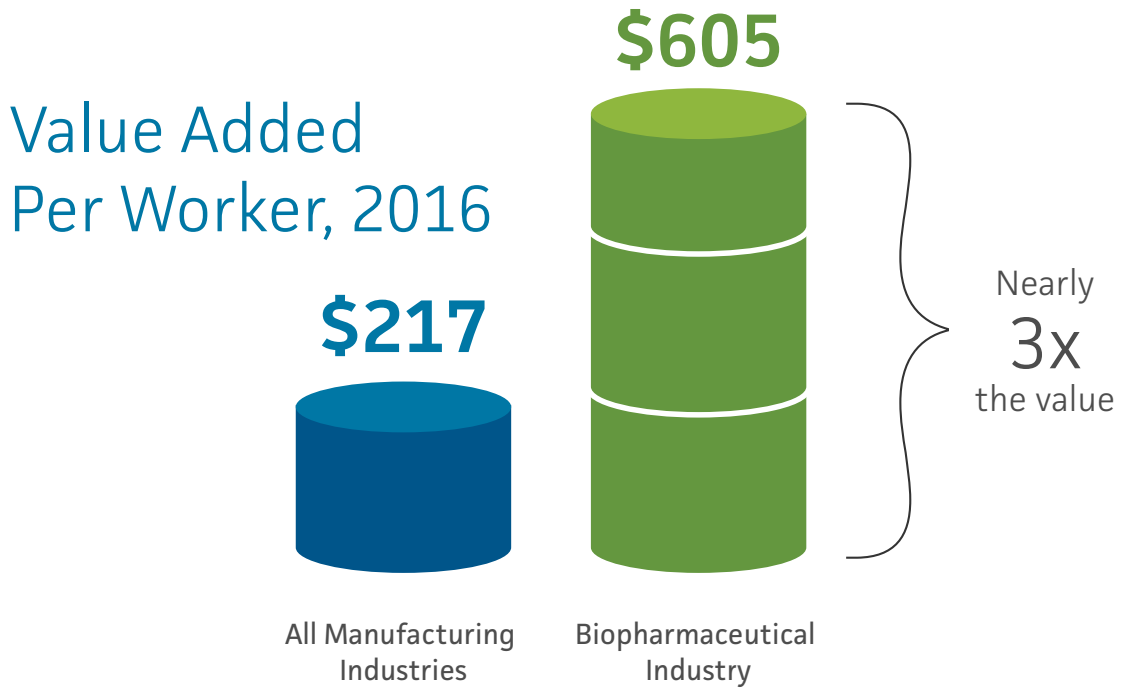
The U.S. biopharmaceutical manufacturing industry has outpaced not just all manufacturing, but all private sector industries over the 2000 to 2016 period in its economic output including during the most recent recession.



Source: U.S. Bureau of Economic Analysis

Sustaining a High Level of Productivity

The biopharmaceutical manufacturing industry stands nearly three times higher in the value of its labor productivity than all manufacturing in 2016, demonstrating its capacity as an economic growth driver. Higher productivity is associated with ability to pay higher wages and to produce more manufacturing output per labor input.

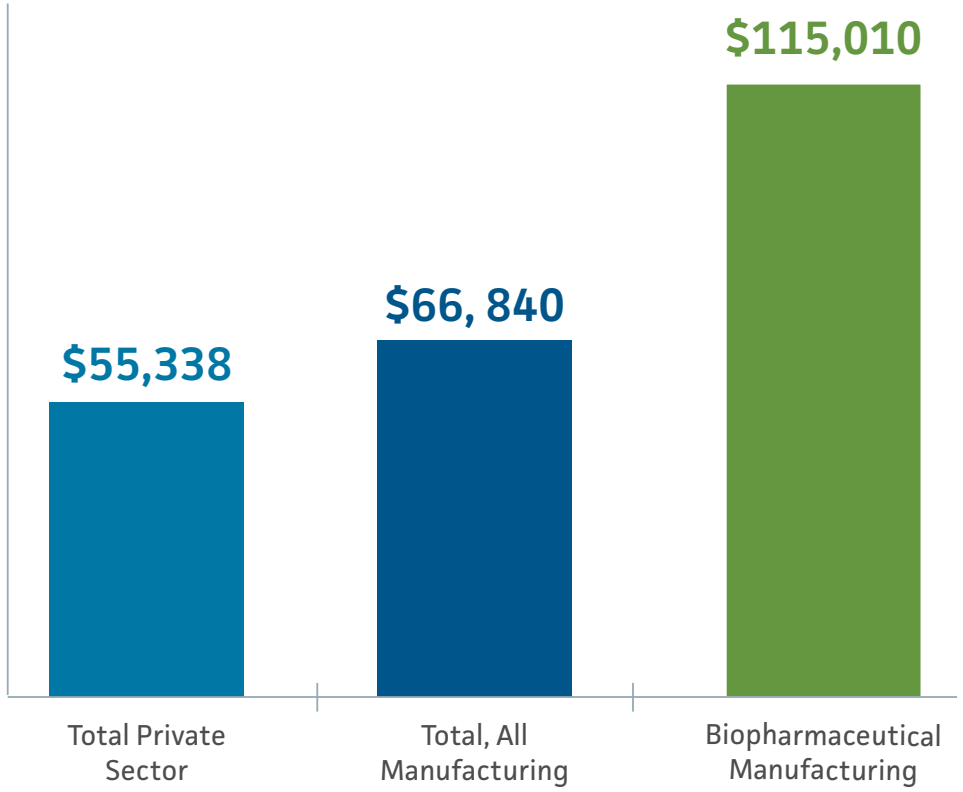


*Value added more precisely considers the economic contribution of manufacturers in designing, processing and marketing the materials they sell compared to just economic output by adjusting for the purchase of other materials, including imported goods, used in the production process.

Source: U.S. Bureau of Economic Analysis

Generator of High-Wage Jobs

The high value of biopharmaceutical manufacturing activities translates into high wages for industry workers. In 2017, average industry wages stood at $115,000.



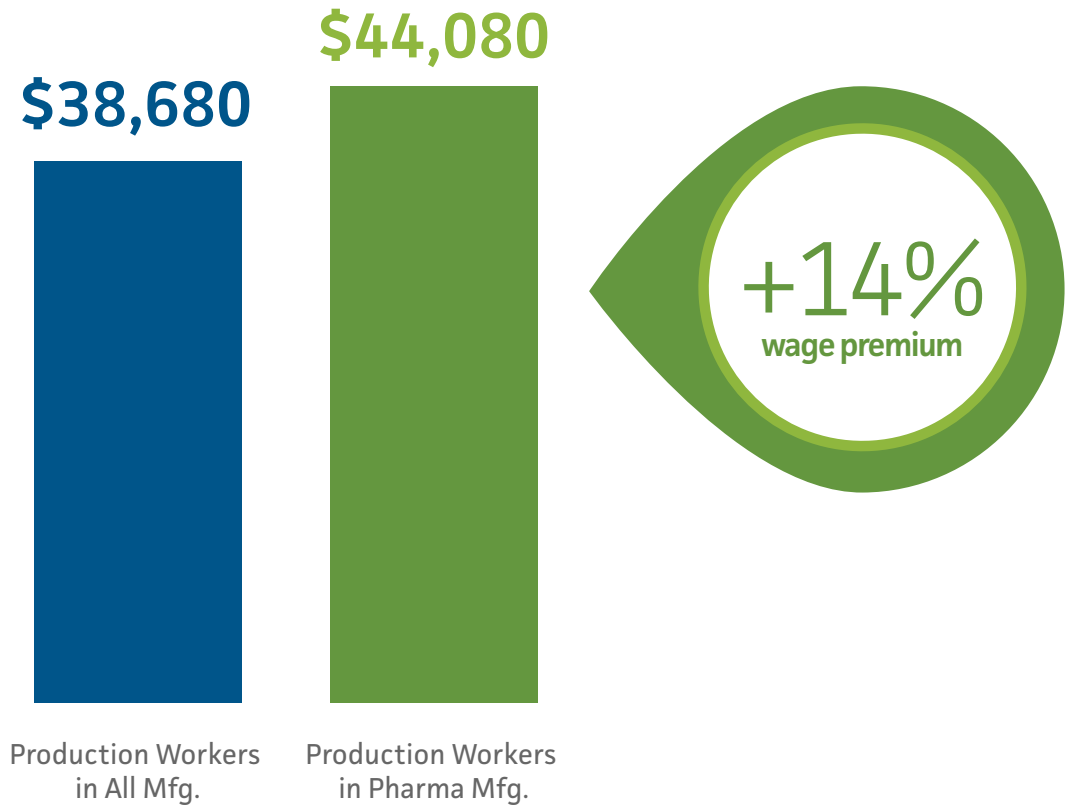
Average Annual Wages, 2017

Biopharma manufacturing wages 72% greater than the average wage for all U.S. manufacturing.

Source: U.S. Bureau of Labor Statistics

High Wages in Production Activities

The strong value-adding activities and productivity of the U.S. biopharmaceutical manufacturing industry are reflected not only in greater overall industry wages, but extending to production workers with a 14% wage premium relative to all manufacturing.



Source: U.S. Bureau of Labor Statistics

Broad Range of Production Occupations

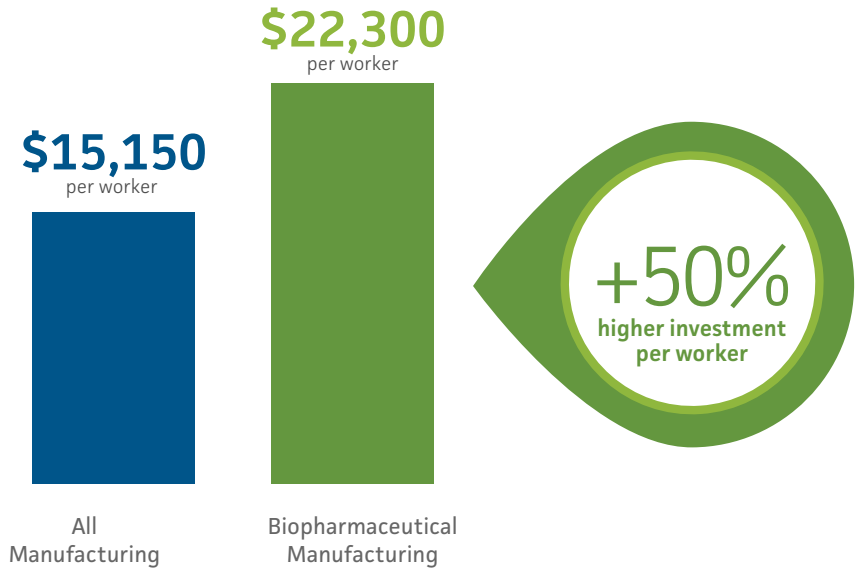
The U.S. biopharmaceutical manufacturing industry supports a wide range of production-related jobs at significantly higher levels of specialization than all manufacturing industries.

Packaging and Filling Machine Operators and Tenders	Mixing and Blending Machine Setters, Operators, and Tenders	Inspectors, Testers, Sorters, Samplers, and Weighers	Chemical Equipment Operators and Tenders	Separating, Filtering, Clarifying, Precipitating, and Still Machine Setters, Operators, and Tenders
25k Industry Jobs	14k Industry Jobs	14k Industry Jobs	11k Industry Jobs	3k Industry Jobs
4x the Concentration of all Mfg.	5x the Concentration of all Mfg.	2x the Concentration of all Mfg.	5x the Concentration of all Mfg.	3x the Concentration of all Mfg.
$34k Avg. Annual Wage	$42k Avg. Annual Wage	$49k Avg. Annual Wage	$45k Avg. Annual Wage	$47k Avg. Annual Wage

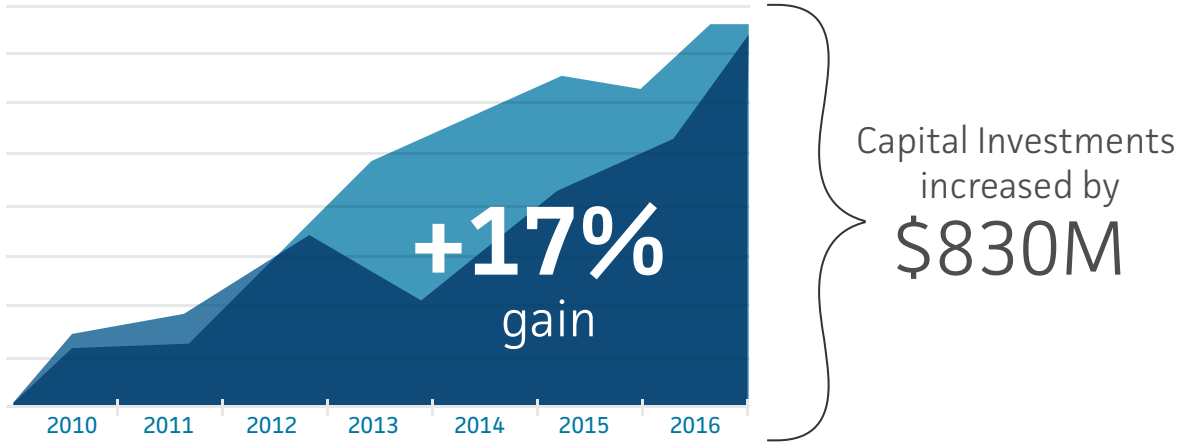
Source: U.S. Bureau of Labor Statistics

Generator of High and Rising Levels of Investment in U.S. Manufacturing Facilities

Biopharmaceutical manufacturing industry invested 50% more in capital expenditures for facilities in 2016



Capital investments in facilities by biopharmaceutical manufacturers rising



Significant Economic Spillovers: Construction Jobs

The high and rising levels of capital investment in biopharmaceutical manufacturing facilities is an important driver of construction activity and jobs in skilled trades.

$22.4 billion
in biopharmaceutical plant construction projects in 11 states from 2012-2017

Generated
45.4 million
construction hours or the equivalent of 23,000 full-time jobs

Highest demand being for electricians, instrumentation techs, plumbers, carpenters and millwrights, each with more than
3 million
construction hours

Source: Russell Ormistron, Research Scholar, Institute for Construction Economic Research and Professor at Alleghany College, Report for Pharmaceutical Industry Labor Management Association, September 2018

Significant Economic Spillovers: Supply Chain of Other Manufacturing Industries

The U.S. biopharmaceutical manufacturing industry relies upon a significant number of manufacturers for inputs into its production process, across the supply chain from packaging, to various ingredients and equipment as well as high-precision measuring and analytic tools, to production automation components.

Packaging, Labeling, & Other Printing

52.2k
Industry Jobs

$63k
Avg. Annual Compensation

Chemical Inputs

11.6k
Industry Jobs

$127k
Avg. Annual Compensation

Production Apparatus & Equipment

4.2k
Industry Jobs

$73k
Avg. Annual Compensation

Electronics, Computers, & Comm. Equipment

4.0k
Industry Jobs

$119k
Avg. Annual Compensation

All Other Manufacturing

36.1k
Industry Jobs

$75k
Avg. Annual Compensation

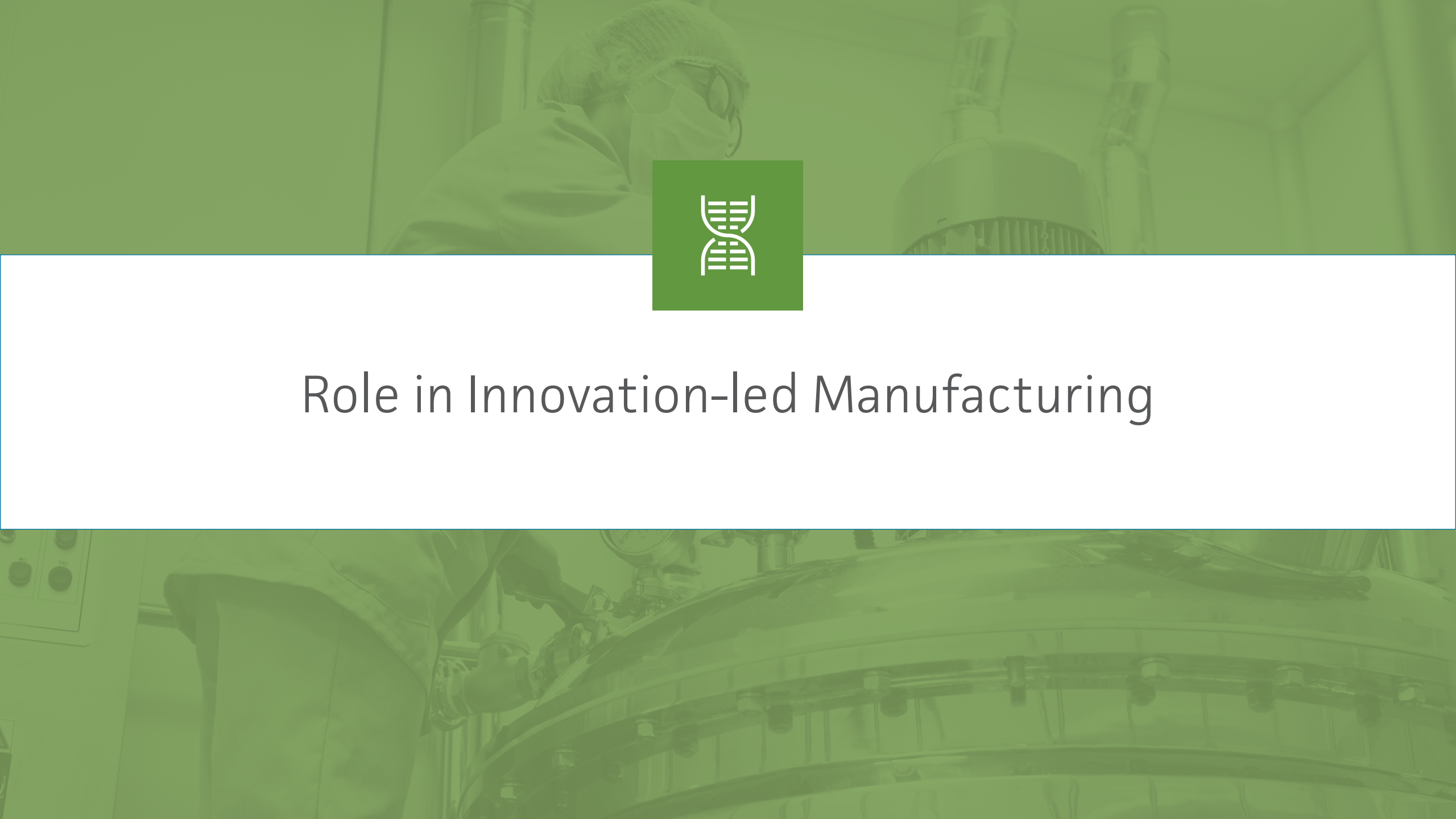
Source: TEConomy, The Economic Impact of the U.S. Biopharmaceutical Industry: 2015 National and State Estimates

A Top Source of U.S. Manufacturing Exporters

Among R&D-intensive manufacturing industries, the biopharmaceutical industry was the largest exporter of goods in 2017.

Industry	Total Exports ($M)
Pharmaceuticals & Medicines	$51,143.50
Navigational/Measuring/Medical/Control Instrument	$37,743.80
Semiconductors & Other Electronic Components	$34,750.40
Communications Equipment	$17,303.90

Source: U.S. Census. USA Trade: Foreign Trade Data, Domestic Exports 2017 and TEConomy analysis.



Role in Innovation-led Manufacturing

Role in Innovation-led Manufacturing

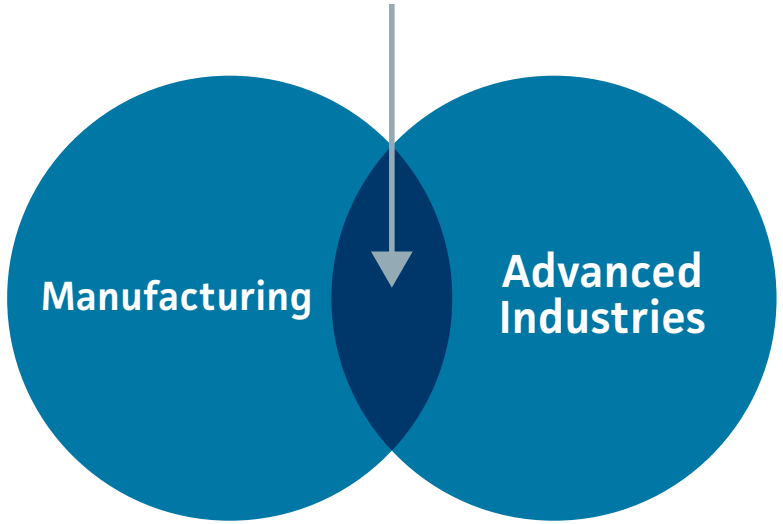
The U.S. biopharmaceutical manufacturing industry belongs to an "elite" grouping of advanced manufacturing industries driven by innovation.

Biopharmaceuticals were one of the 35 identified advanced industries based on high levels of R&D spending per worker and share of workers in Science, Technology, Engineering and Math (STEM) occupations in a study by the Brookings Institution and McKinsey & Company

Biopharmaceuticals were one of the 38 advanced industries identified as intellectual property (IP)-intensive by the U.S. Commerce Department and U.S. Patent and Trademark Office.

Being both a leading manufacturing industry and an advanced/IP-intensive industry enables the biopharmaceutical manufacturing industry to generate significant economic benefits as a growth driver for the U.S. economy.

Innovation-Led Manufacturing Leads the Way



Manufacturing Benefits:

- High quality jobs across a mix of skills
- Significant supply chains that magnify job creation potential as production rises
- Export oriented

Advanced Industries' Benefits:

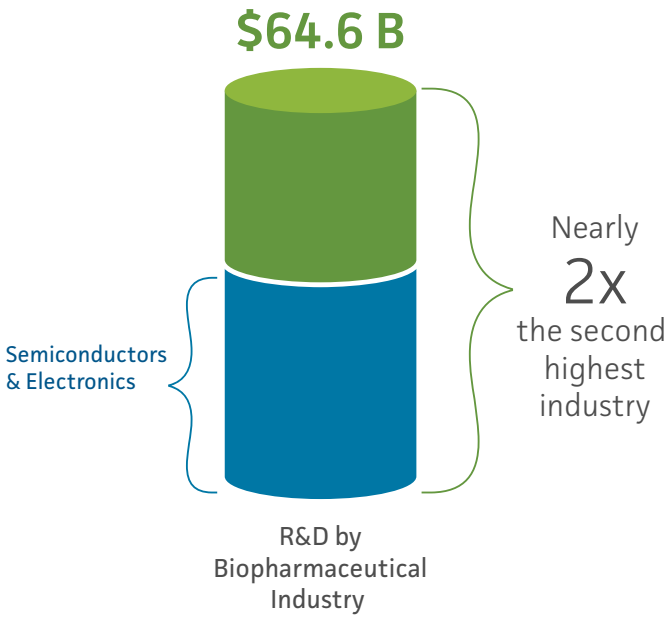
- Leading industries in innovation
- Deploy science, technology, engineering and math skills
- Most competitive industries in U.S.
- High productivity

Sources: Brookings Institution, America's Advanced Industries: What They Are, Where They Are and Why They Matter, 2012 and U.S. Commerce Economics and Statistics Administration and U.S. Patent and Trademark Office, Intellectual Property and the U.S. Economy: 2016 Update

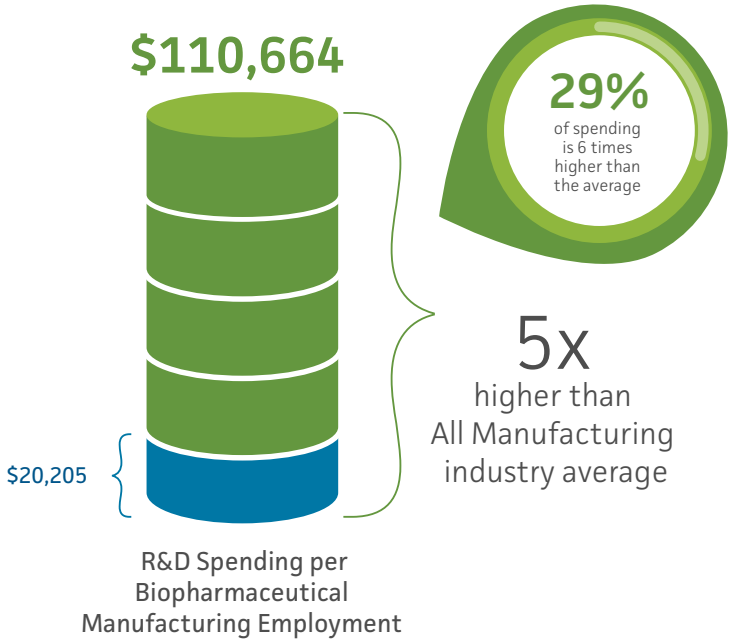
Leader in U.S. Research & Development

R&D is closely tied to manufacturing in advanced manufacturing industries. Biopharmaceuticals are a leader in the level, intensity and growth of research and development.

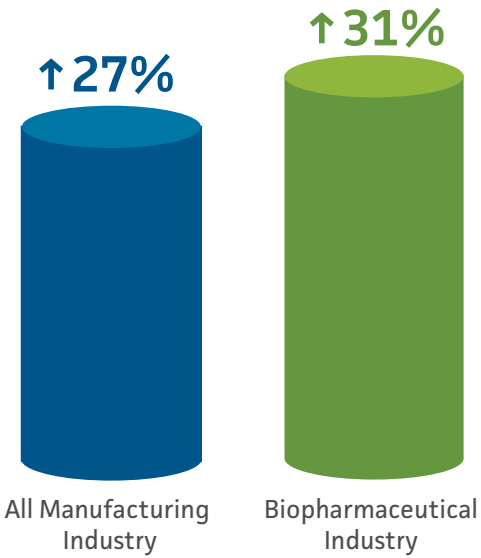
Level of R&D
2016



Intensity of R&D
2016



Growth of R&D
2010-2016



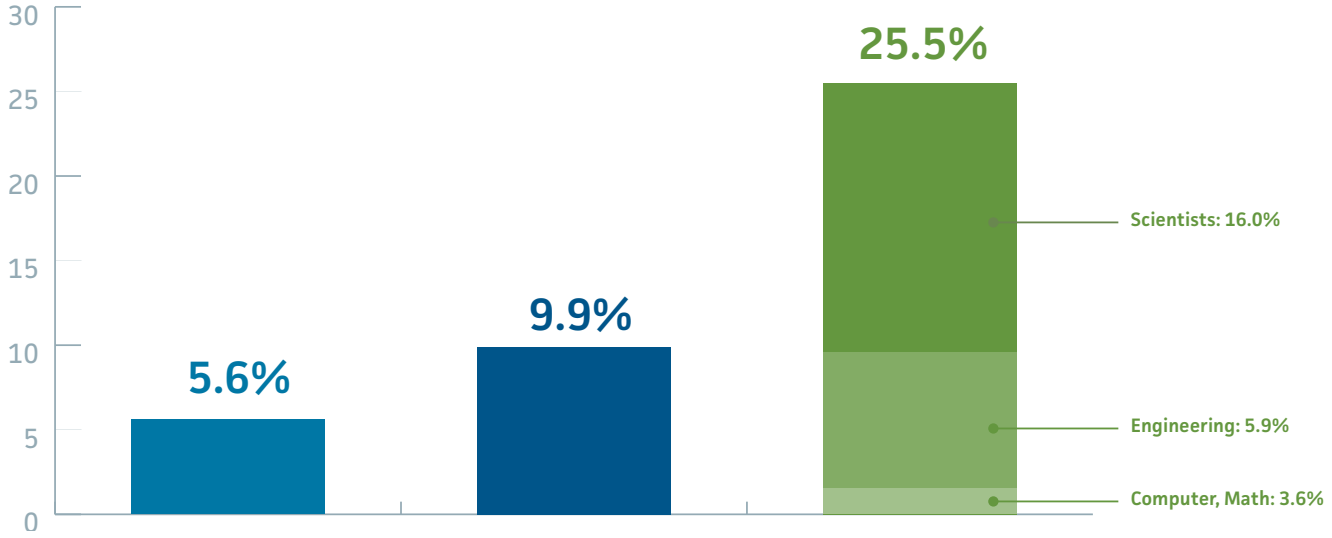
Source: National Science Foundation, Business R&D and Innovation Survey, 2016; Calculations of R&D employment by TEConomy

Leader in STEM Workforce

The biopharmaceutical manufacturing industry stands out in its level and concentration of "STEM" workforce – more than double the level of all U.S. manufacturing and **nearly 5 times** that of all private sector industries.

Biopharmaceutical manufacturers utilize an especially high concentration of scientific occupations **(16% of all industry jobs compared with just 1% for all manufacturing).**

Share of Industry Employment in "STEM"-related Occupations, 2017



Source: U.S. Bureau of Labor Statistics, Occupational Employment Statistics, Calculations by TEConomy

Broad Impacts of Innovation Ecosystem Involving Biopharmaceutical Manufacturing Industry

As both a manufacturing and advanced industry, U.S. biopharmaceutical manufacturing does not stand alone but is part of a larger innovation complex required to discover, develop, produce and distribute medicines to patients.

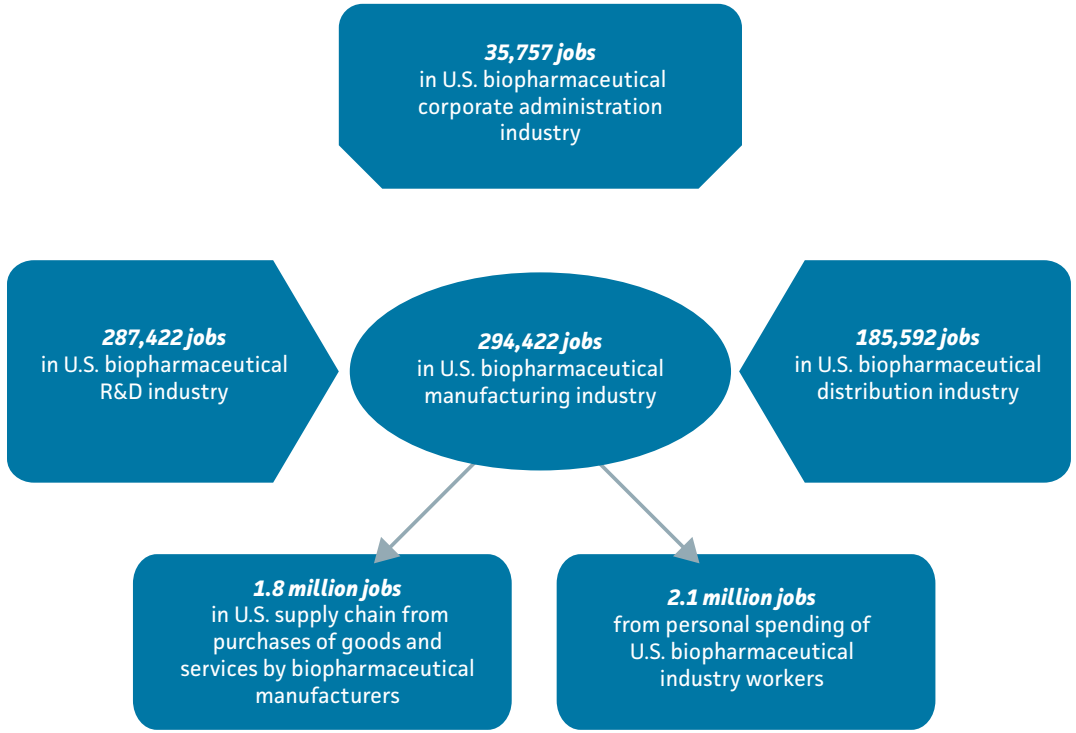
For every one worker employed in the biopharmaceutical manufacturing industry another 4.9 jobs are generated across a range of other industries.

Other closely-related specialized biopharmaceutical industries that are core to the functioning of the U.S. biopharmaceutical innovation ecosystem are:

- Contract research organizations, start-ups, and early stage biopharmaceutical companies
- Industries involved in implementing a complex specialized biopharmaceutical distribution system

As a result, the U.S. biopharmaceutical manufacturing has significant economic spillover effects through:

- A vast supply chain of other manufacturers and service providers.
- High wages paid to biopharmaceutical workers leads to personal spending on goods and services for an even broader range of industries in the U.S.



Source: TEConomy, The Economic Impact of the U.S. Biopharmaceutical Industry: 2015 National and State Estimates

Specialized, Highly Regulated Processes for Biopharmaceutical Manufacturing

Specialized, Highly Regulated Processes for Biopharmaceutical Manufacturing

Biopharmaceutical manufacturing provides the critical link between the discovery of a medicine and its availability to a patients

Reflecting its close connection to scientific discovery, the processes involved in biopharmaceutical manufacturing are complex and evolving. While the overall process of producing a medicine has common elements, biopharmaceutical manufacturing is further complicated by having two broad manufacturing platforms reflecting the two broad classes of medicines that existing – one based in chemistry and the other in biology.

By necessity, all biopharmaceutical manufacturing is conducted under especially high standards, with strict requirements and rigorous approvals by the U.S. Food and Drug Administration to ensure the safety, quality and reliability of the manufacture of medicines to protect patients and deliver the intended therapeutic benefits.

"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 or biology to synthesize the molecule, and new or improved facilities and equipment to transform living material into a medicine."

Deloitte, "Advanced Biopharmaceutical Manufacturing: An Evolution Underway, 2015"

Biopharmaceutical Manufacturing Methods Driven by Science

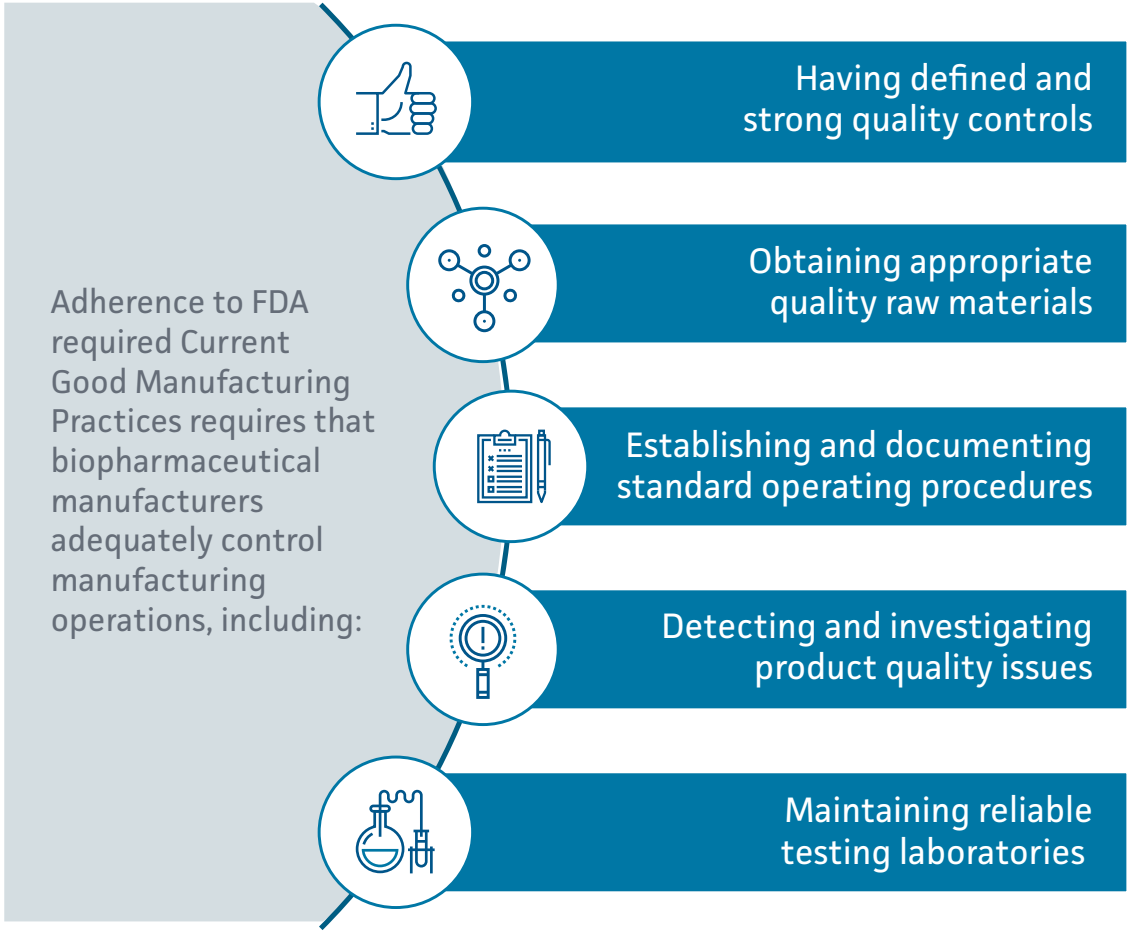
While the manufacture of biopharmaceuticals involves a common set of production steps, there are two primary manufacturing platforms. One reflects the science behind small-molecule medicines manufactured using chemical synthesis; the other consists of large-molecule biologic medicines manufactured using living cells.

	SYNTHESIS/ENGINEERING	PURIFICATION	FORMULATION	QUALITY & PROCESS CONTROL
Small Molecule, Chemistry-based Production Platform	Use of chemical synthesis that assembles the required chemical structure through well-defined and replicable steps	Able to utilize highly advanced analytical tools to guide the isolation and concentrate the active pharmaceutical ingredient from other chemicals left over from the synthesis reactions	Able to blend active ingredients with other chemical-based fillers into highly stable tablets or capsules forms that can be packaged and not require specialized handling	Highly replicable process to be monitored through use of analytical tools ensuring production of unique, though well-defined molecular structure
Large Molecule, Biology-based Production Platform	Involves living entities such as cells and tissues being isolated from a variety of natural resources and may be produced by biotechnology methods and other cutting-edge technologies.	Involves use of filtration approaches that require ongoing optimization due to variability from batch to batch in order to separate living cells from cellular nutrients and byproducts	Remains in a liquid or frozen forms and delivered through injection or infusion and so must be kept sterile and is highly sensitive to temperature conditions	Given complexity of the molecular structure and inherent variability of scaling up living cells, quality control requires focus on comparability of biological activity.

All Medicines Sold in U.S. are Held to a High Standard for Quality in Manufacturing

To a degree unmatched in other manufacturing industries, the biopharmaceutical manufacturing industry faces extensive strict regulatory standards. Biopharmaceutical manufacturing facilities are inspected by the U.S. Food and Drug Administration (FDA) to ensure that the facility is able to maintain the quality (i.e., the identity, strength, and purity) of the drug products it manufactures.

- Biopharmaceuticals manufacturers are required to implement and maintain necessary controls to ensure product quality.
- FDA inspects biopharmaceutical facilities that manufacture medicines intended for U.S. patients to ensure adherence to high manufacturing quality standards.

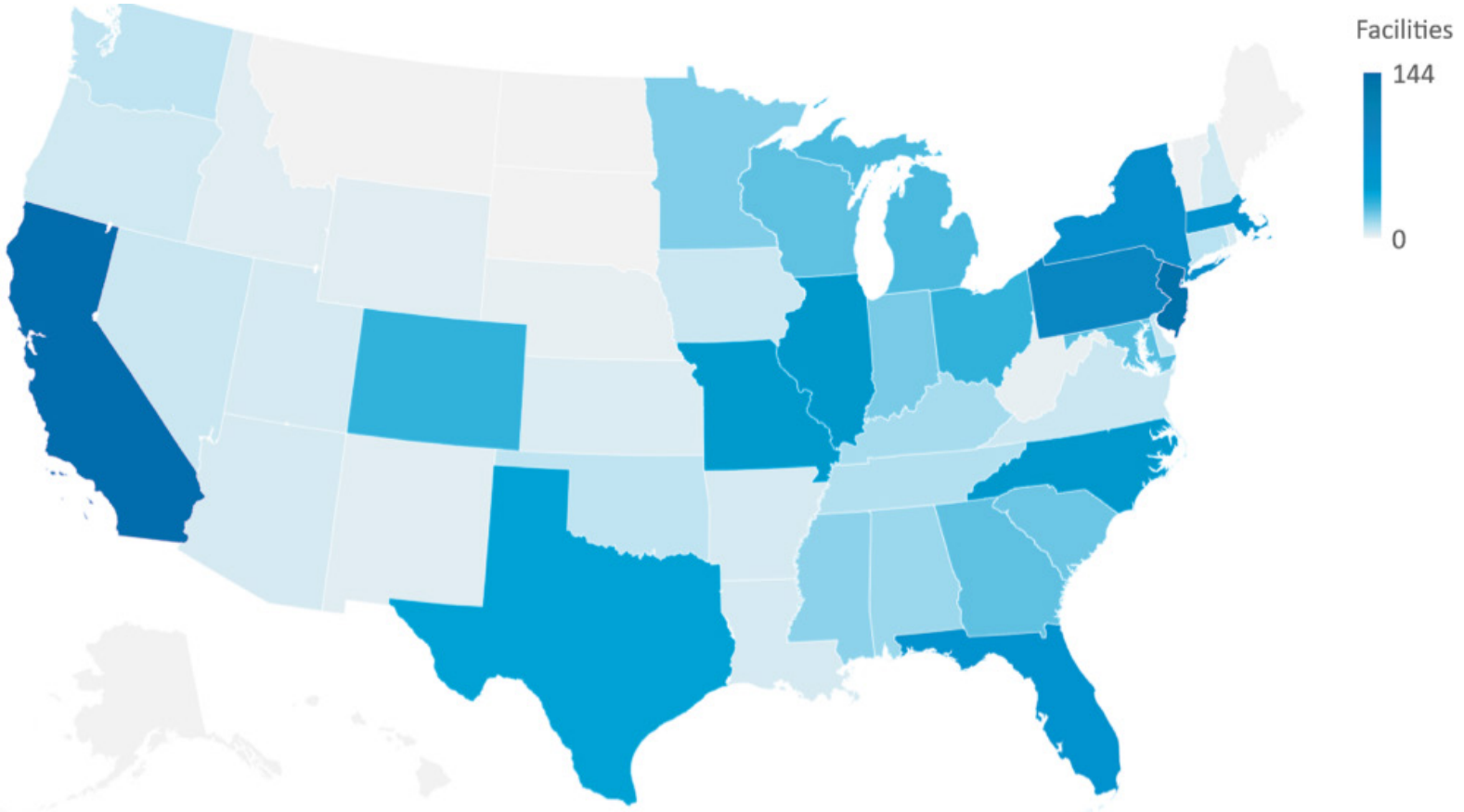


Source: FDA, "Facts About the Current Good Manufacturing Practices" last updated June 25, 2018

Nearly All States are Involved in the Manufacturing of FDA-Approved Medicines

Currently 1,193 facilities in the US are manufacturing FDA-approved products under current Good Manufacturing Practice regulations.

- These facilities are spread across 44 states, the District of Columbia and Puerto Rico
- 37 states and Puerto Rico have 5+ facilities manufacturing FDA-approved medicines



Source: NDP Analytics; for PhRMA. Analysis of the U.S. Food and Drug Administration's Drug Establishments Current Registration Site. April 2018

Manufacturing Process Innovations are Often as Important as New Product Innovations

"[T]here are relatively few high-tech industries where the manufacturing process is not a factor in developing new – especially, radically new – products. That's because in most of these industries product and process innovation are intertwined."

--Pisano, GP and Shih, WC, "Restoring American Competitiveness," Harvard Business Review, 2009.

Biopharmaceutical manufacturers constantly innovate and adopt new technologies to keep pace with scientific advances made through R&D, to advance R&D capabilities, and to maintain competitiveness in a changing regulatory and reimbursement environment. Without this, manufacturers would not be able to produce the complex yet impactful new medicines of today. Areas of innovation in biopharmaceutical manufacturing include:

- Continuous Manufacturing
- Single-Use Systems
- High-Volume Cell Processing Advances
- Advanced Purification Technologies
- Cell Preservation, Distribution and Handling Methods

Examples of Innovative Manufacturing Solutions: Continuous Manufacturing

Challenge: Produce greater quantities of products more quickly is a key challenge.

Solution: Continuous Manufacturing

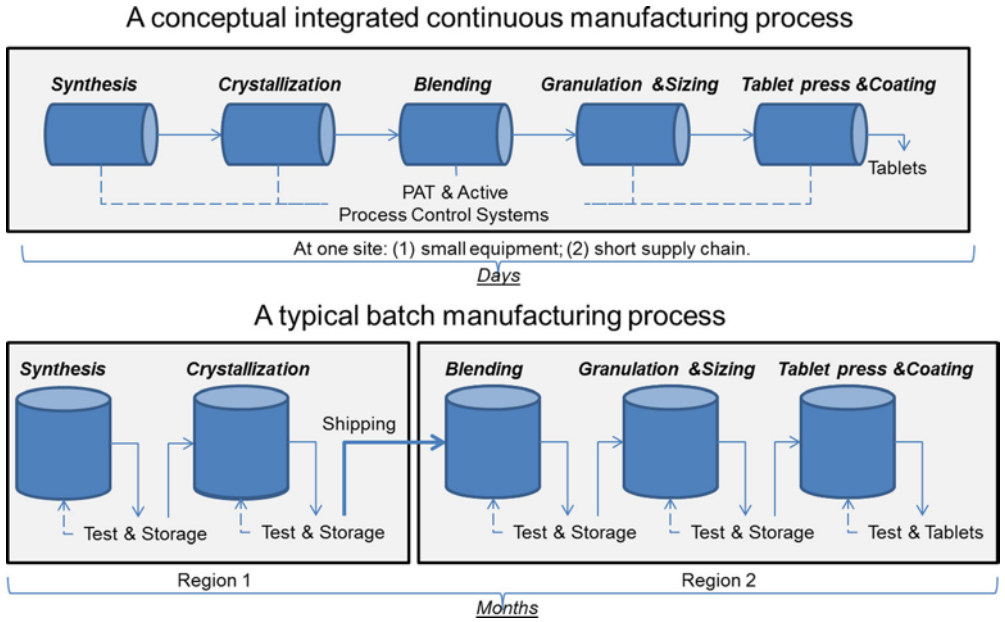
Instead of manufacturing in batches, continuous manufacturing involves a fully integrated process in the production of medicines that offers the potential to improve scalability and facilitate time to market, and enhance product quality.

While this is not the solution for all medicines, it can provide efficiencies where appropriate.

The transition to continuous manufacturing is still in its early phases and faces obstacles including:

- Start-up costs for such a transition can be high – including purchasing new technology, revamping plant infrastructure and training staff
- For some types of drugs, such as biologic medicines, additional technologically challenges remain
- Regulatory uncertainty hampers investment – currently no clear, consistent regulatory pathway defined by FDA

Example of Continuous Manufacturing for Small-Molecule Chemistry-based Medicines



Source: "Sau (Larry) Lee, Modernizing the Way Drugs Are Made: A Transition to Continuous Manufacturing," Spotlight on CDER Science, FDA, last updated May 17, 2017; Deloitte, "Advanced Biopharmaceutical Manufacturing: An Evolution Underway," 2015

Examples of Innovative Manufacturing Solutions: Single-Use Systems

Challenge: Biopharmaceutical manufacturing facilities producing large molecule medicines require significant time and investment in such aspects as sterilizing equipment, bioreactor systems and accessories between production runs, and depending on the size of the facility, may have limited ability to manufacture multiple products at one facility given the substantial complexity, time and investments required.

Solution: Single-Use Systems

Involves use of disposable components replaced after each use in the manufacturing process. Can be used at nearly every step of the production process, such as disposable tubing and filtration, single-use bioreactors and single-use diagnostic arrays.

A key advantage of single-use systems is creating flexibility in using the same floor space to manufacture different types of low volume products, reduce production lead times, and lower capital investment and resource requirements.

Some of the barriers in the use of single-use systems include:

- Size of production runs are often limited in single-use systems
- Use of plastic disposables creates validation issues based on materials used by suppliers
- Challenges related to disposal

Sources: Deloitte, "Advanced Biopharmaceutical Manufacturing: An Evolution Underway", 2015; Image from Millipore Sigma

Examples of Innovative Manufacturing Solutions: High-Volume Cell Processing Advances

Challenge: Current methods of cell processing are not keeping up with the development of new cell-based medical products that introduce living cells to replace or repair damaged or diseased cells, such as in acute diseases such as stroke or spinal cord injury. One of the biggest challenges in the advancement of cell-based therapies is developing large-scale manufacturing processes that ensure the potency, consistency and safety of the cells at an economically viable cost.

Solution: High-Volume Cell Processing Advances

To support the manufacture of a variety of new cell-based medicines, next-generation cell expansion technologies are being advanced to enable high-volume cell processing. These include:

- Advancement of automated, closed bioreactor systems that can more closely monitor and adjust the process of cell expansion utilizing advanced data analysis and modeling tools
- Use of bioreactors with parallel processing capabilities to increase manufacturing throughput and shorten processing time
- Use of novel high-yield culture media alternatives to optimize cellular productivity

Example of a Parallel Bioreactor System

Source: National Cell Manufacturing Consortium, "Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells: A Technology Roadmap to 2025," February 2016; Image from Sartorious

Examples of Innovative Manufacturing Solutions: Advanced Purification Technologies

Challenge: A critical component of large molecule manufacturing is purification. Purifying the product removes "junk" and potentially harmful materials ensuring that only the target molecule is collected at the end of the manufacturing process. The purification process is extremely complex, resource intensive, and time consuming. Because of these challenges, manufacturers are constantly seeking new ways to reduce the process bottlenecks created by the purification process while maintaining product quality and purity..

Solution: Advanced Purification Technologies

- New innovative chromatography tools and resins as well as chromatography free purification methods are designed to remove processing bottlenecks, introducing numerous efficiencies throughout the manufacturing process and resulting in greater yields and speeding up production.

- New technologies for purification of biological fluids could provide biopharma enterprises with membranes having high permeability, allowing very fast flow rates and uniform pore sizes for extremely precise nanofiltration.

Source: Laura Elizabeth Mason, "Protein Purification: Chromatography and Scalability in Biopharma," Technology Networks: Biopharma, November 21, 2017; Theresa Phillips, "Methods for Protein Purification in Biotechnology," The Balance, December 23, 2018; AbiSci, http://www.absci.com/; Deloitte, "Advanced Biopharmaceutical Manufacturing: An Evolution Underway," 2015

Examples of Innovative Manufacturing Solutions: Cell Preservation, Distribution and Handling Methods

Challenge: As manufacturers implement the Drug Supply Chain Security Act (DSCSA), product packaging is being updated to allow for greater traceability of biopharmaceutical products. However, for certain cell-dependent products such as biologics and gene- and cell-based therapies, there are distribution challenges that go beyond supply chain security. Manufacturers are faced with the challenge of maintaining products in transit at specific temperature ranges, as well as developing more cost-effective preservation methods that are able to ensure the stability of high volumes of the cells and/or product over long periods of time. In some cases, costs of cell product distribution can be higher than the manufacturing costs.

Solutions: A range of approaches are being explored to increase efficiencies

- **Advanced cryopreservation technologies,** which facilitate more precise control of freezing and thawing, informed by increased understanding of the impact of this process on cells.
- **Alternative preservation technologies** for cell types, such as skin cells, that do not maintain potency after being frozen.
- **Complex product tracking systems,** which make use of automated, real-time tracking procedures of the chain of custody and which record bioinformatic-based information to ensure that the correct cells are administered to the correct patient.
- **Enhanced cell bank storage infrastructure** to establish cell supplies that can meet increased demand and to improve stability of master cell banks and optimum size of master cell banks.

Source: National Cell Manufacturing Consortium, A Technology Roadmap to 2025, February 2016

Manufacturing Innovations Driving Startup Formation

New or improved process technologies and methods from startup enterprises backed by venture capital investors are another source of innovation in biopharmaceutical manufacturing.

BIOPHARMACEUTICAL STARTUPS

2000-2018

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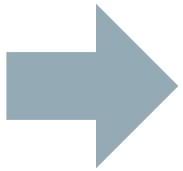
*biopharmaceutical startups involved in the development of manufacturing processes or related activities.**



$2.9 B

raised in venture capital-backed investments.

Case Example:
A venture-backed company received the first FDA approval for a medicine to treat epilepsy manufactured using a 3-D printing process. Made as a porous formulation, the pill is made to be easier for patients to swallow.**

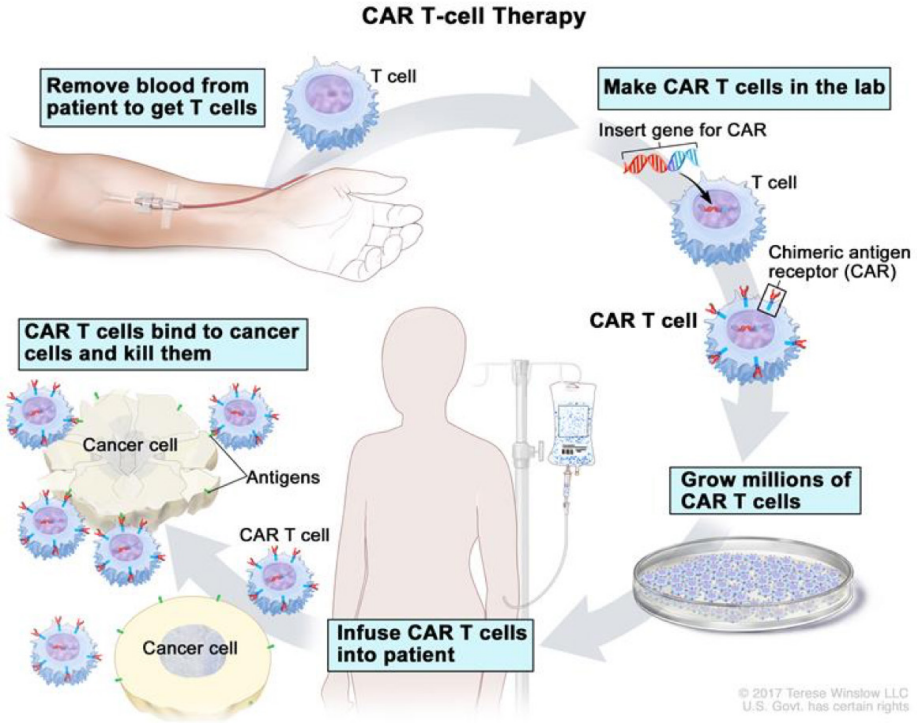
*Out of more than 3,300 U.S. biopharma startups from PitchBook's database, 68 companies were tagged with the Discovery Tools (Healthcare) industry classification ("Tools used in drug discovery and drug delivery research. Includes compound libraries, enzymes, kinases, and specialized proteins, among others."), and 46 additional came from the other subsectors of PitchBook's Pharmaceutical and Biotechnology industry classification.

**Morrison J, "U.S. Food & Drug Administration Approves First 3-D Printed Drug," Chemical & Engineering News, August 5, 2015.

Emerging Areas for Manufacturing Innovation: CAR T Cell Therapy

CAR T is a new class of biologics-based cell therapies being advanced as an immunotherapy to attack cancer cells. It involves using patients' own immune cells, known as T cells, to treat their cancer.

How it works: The T cells are taken from the patient's blood, then the gene for a special receptor – called a chimeric antigen receptor (CAR) that binds to the patient's cancer cells -- is inserted into the T cells in the laboratory and then millions of the CAR T cells are grown in the laboratory.



Challenges for manufacturing CAR T cell therapies:

Not a mass-produced therapy, but one that needs to be individually manufactured for a patient on demand.

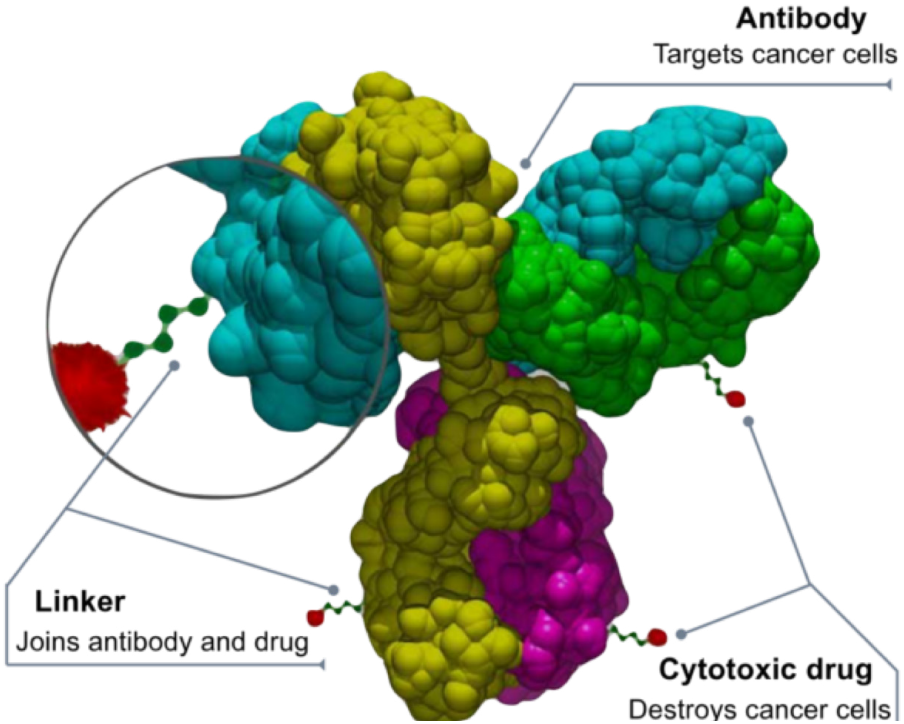
- Manufacturing requires a complex, multi-step process in which a patient's own T cells need to be isolated, activated, reprogrammed and scaled up to produce a therapeutic dose
- Logistics challenges are many throughout the process of T cell extraction, cryopreservation and transport to the manufacturing facility, modification, and then transport to and infusion into patient.

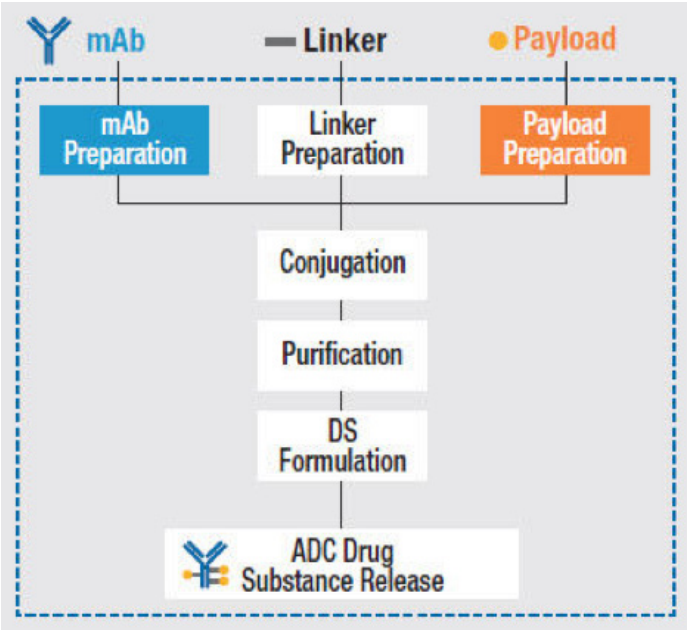
Source: National Cancer Institute's Dictionary of Cancer Terms and factsheet on CAR T Cells Engineering Patients' Immune Cells to Treat Their Cancers and from Cathy Yarbrough, "Intricate Supply Chain Complicates Gene Therapy Manufacturing," Life Science Leader, March 7, 2018

Emerging Areas for Manufacturing Innovation: Production of Antibody-Drug Conjugates

Antibody-drug conjugate (ADC) technology may provide a potentially new therapeutic solution for cancer treatment. ADC technology uses an antibody-mediated delivery of cytotoxic drugs to the tumors in a targeted manner, while sparing normal cells.

Challenge for manufacturing ADC therapies: The biggest challenge is ensuring that in the integration of three essentially different manufacturing processes, that the product consistently meets required purity standards and is safe from environmental and process related contamination.





Source: Images from https://en.wikipedia.org/wiki/Antibody-drug_conjugate and https://www.novasep.com/home/products-services/pharma/cmo-for-api-and-cytotoxic/antibody-drug-conjugates-manufacturing.html

Emerging Areas for Manufacturing Innovations: Green Chemistry To Create Energy Efficiencies and Minimize Environmental Impacts

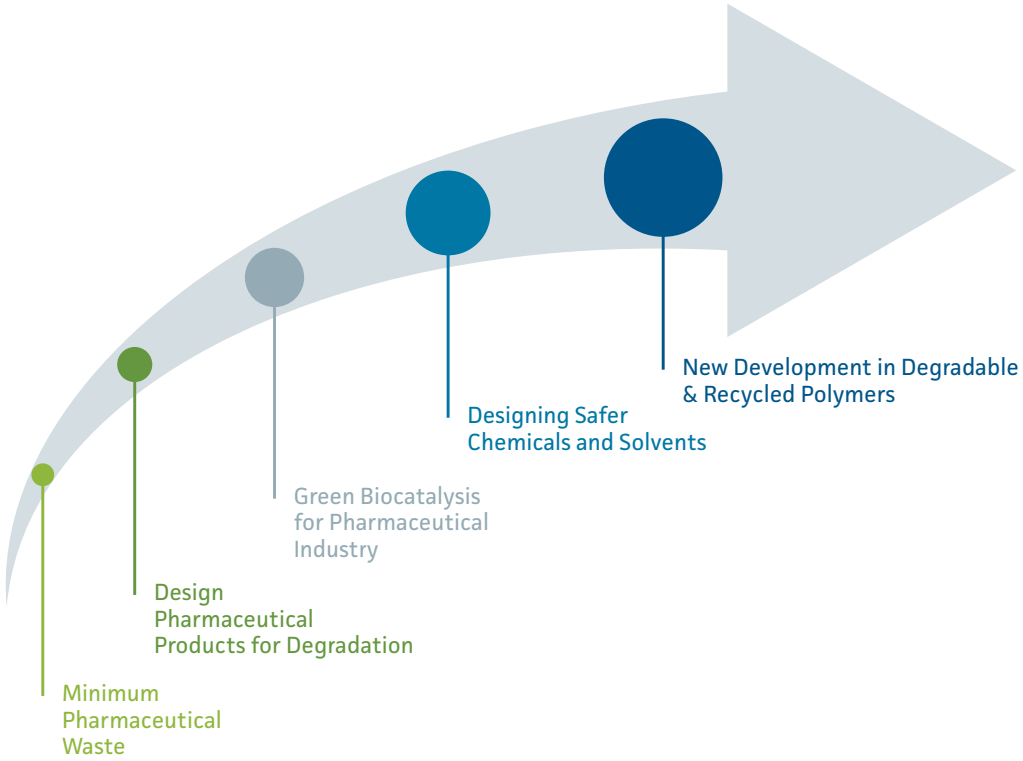
Green chemistry focuses on continued innovation to reduce waste, require less use of energy, and minimize environmental impacts in all aspects of biopharmaceutical manufacturing

"The pharmaceutical industry has embraced green chemistry more so than others … Pharma companies tend to be research-based organizations who are interested in optimizing their chemistry."

- David Constable, Director of the American Chemical Society's Green Chemistry Institute

In the biopharmaceutical manufacturing industry, two key areas of focus are:

- Replacing solvents with safer alternatives and designing processes that have lower carbon footprints and reduce emissions and energy use.
- Using natural or genetically engineered enzymes that are renewable and biodegradable as catalysts.



Source: See discussion in Deloitte, Advanced Biopharmaceutical Manufacturing: An Evolution Underway, 2015; Graphic from Deepali and Kori, Department of Pharmaceutical Science, Singh Post Graduate Institute of Biomedical Science & Research

U.S. is a Global Leader in the Biopharmaceutical Manufacturing Industry, but Competition is Rising

U.S. is a Global Leader in the Biopharmaceutical Manufacturing Industry, but Competition is Rising

The U.S. biopharmaceutical manufacturing industry leads the world through its integrated innovation ecosystem, but international competitors are closing the gap.

While the U.S. still remains the world's preeminent powerhouse in biopharmaceutical manufacturing, the trends since 2010 suggest that in all but a few areas of activity, the U.S. is not keeping pace and so is losing ground to international competitors.

"The United States' lead in the life sciences is being challenged. Other countries have aggressively courted life-sciences companies with lower tax rates, a range of firm-specific tax benefits, increased government research funding, improved intellectual property protections and streamlined approval processes."

ITIF, "How to Ensure That America's Life-Sciences Sector Remains Globally Competitive, March 2018

U.S. is the Global Leader in Biopharmaceutical Value Added, but China is Gaining Fast

The U.S. has remained the global leader in biopharmaceutical value added, with $127.3 billion – nearly one-quarter – of the world's overall value added. Value added is a key measure of the level of economic activity in a given area. China has nearly caught up to the U.S., and grew 5 times faster than the U.S. over the 2010-2016 period.

	2016 Biopharmaceutical Value Added ($ billions)	Percentage Growth in Biopharmaceutical Value Added, 2010-2016
United States	$127.30	30.40%
China	$118.50	150.40%
World	**$535.40**	**33.60%**

Source: NSF Science and Engineering Indicators, 2018 based on data from IHS Global Insight, World Industry Database, accessed July 17, 2017

U.S. Dominates in Global Biopharmaceutical Venture Capital Investments

With over 70% of global biopharmaceutical venture capital investments, the U.S. stands apart from its global competitors. China is making strong gains, but at $1.9 billion in 2017, is a mere 16% of the U.S.'s global-leading $12.1 billion in biopharmaceutical venture capital investment.

	2017 Biopharmaceutical Venture Capital Investment ($ billions)	Percentage Growth in Biopharmaceutical Venture Capital Investment, 2010-2017
United States	$12.10	166%
China	$1.90	1084%
United Kingdom	$0.60	116%
World	**$16.90**	**168%**

Source: Pitchbook, Calculations by TEConomy

U.S. has a Strong Lead in Biopharmaceutical Patents, but Faces Increasing Competition

The U.S. accounted for nearly twice as many global patents in 2017 as its nearest competitor, China.

The U.S. is exceeding worldwide growth of biopharmaceutical patents, reflecting the high level of innovation in the R&D and manufacturing processes for biopharmaceuticals. While this is an area of continued competitive advantage, China is becoming increasing competitive as is South Korea.

	2017 Biopharmaceutical Patents	Percentage Growth in Biopharmaceutical Patents, 2010-2017
United States	19,864	57%
China	10,243	56%
South Korea	4,888	211%
World	**65,262**	**45%**

Source: World Intellectual Property Organization (WIPO) statistics database. Includes all patents issued by members of WIPO based upon applicant's origin (equivalent count). Last updated: December 2018. Biopharmaceutical consists of WIPO Biotechnology and Pharmaceuticals Technology Fields.

U.S. Biopharmaceutical Industry R&D Activity Well Outpaces Global Competitors, but Emerging Nations Are Growing Fast

The U.S., at $58.7 billion in biopharmaceutical industry R&D activity in 2015, was three times larger than its closest competitor, Japan, at $14.2 billion.

As in other areas of biopharmaceutical development, China is out in front in growth rate with a gain of 152% from 2010-2015, bringing its total level of biopharmaceutical industry R&D activity to $12.7 billion in 2015.

	2015 Biopharmaceutical Industry R&D	Percentage Growth in Biopharmaceutical R&D, 2010-2015
United States	$58.70	19%
Japan	$14.20	24%
China	$12.70	152%
South Korea	$1.60	77%

Source: OECD Main Science & Technology Indicators, accessed December 7, 2018. Data compares R&D performed by pharmaceutical manufacturing sector in each country for 2015, the most recent common year available. A more comprehensive measure of U.S. biopharmaceutical industry R&D, including human biotech, would be $85.3 billion in 2015. (Research!America U.S. Investments in Medical and Health Research and Development 2013 – 2017)

Continued U.S. Global Leadership Depends on Having the Right Policies to Support Biopharmaceutical Manufacturing Industry

Senior-level strategic planning executives from U.S. biopharmaceutical companies representing 3/4ths of our nation's biopharmaceutical economic activity identified three policy areas critical for the U.S. biopharmaceutical industry to remain a leading global location for biopharmaceutical manufacturing and R&D:

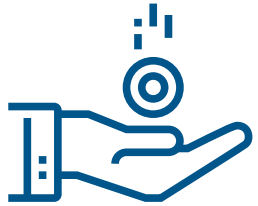
1.

Strong
INTELLECTUAL PROPERTY
protections, including patent and data protection

2.

A well-functioning and evidence-based
REGULATORY SYSTEM

3.



COVERAGE & PAYMENT POLICIES
that support and encourage medical innovation

Source: Battelle, The U.S. Biopharmaceutical Industry: Perspectives on Future Growth and the Factors that Will Drive It, 2014