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TRENDS AND ANALYSIS FOR THE BIO/PHARMA INDUSTRY — 15 YEARS

FIFTEENTH ANNUAL

Report and Survey of Biopharmaceutical Manufacturing Capacity and Production

A Study of Biotherapeutic Developers and Contract Manufacturing Organizations

APRIL 2018

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April 2018

BioPlan Associates, Inc.
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15th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production

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- Dave Backer, Head of Commercial Development, Gene Editing & Novel Modalities, MilliporeSigma
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- Nigel Darby, former Vice President, Bioprocess, GE Healthcare Life Sciences
- David Deere, Chief Commercial Officer, PaizaBio
- Amit R. Dua, Global Marketing Strategy Leader, Bioprocess, GE Healthcare Life Sciences
- Parrish M. Galliher, Chief Technology Officer, Upstream, GE Healthcare Life Sciences
- Gunter Jagschies, Senior Director, Strategic Customer Relations, GE Healthcare Life Sciences
- Ying Jing, Sr. Strategy and Technology Leader, Cell Culture, Novartis Pharma AG
- Morten Munk, Global Technology Partner, NNE A/S
- Kent Payne, CEO, Socorro Pharmaceuticals, LLC
- Stefan Schmidt, Chief Scientific Officer, Rentschler Biopharma SE
- Joseph Shultz, Head of Advanced Process and Manufacturing Technologies, Novartis Pharma AG
- Christoph Winterhalter, Senior Vice President, Business Development, AGC Biologics

We would also like to recognize our Institution Partners, and our Media Sponsors. Their efforts in assuring the cooperation and participation in the survey of their respective memberships helped guarantee the large group of survey participants to ensure data accuracy.

Our ***Institution Partners,*** all of whom contributed their time and effort to ensure the broad, international coverage of this project, include:

- AusBiotech (Malvern, Victoria, Australia)
- Beijing Pharma and Biotech Center (Beijing, China)
- BIO (Biotechnology Industry Organization, Washington, D.C.)
- Bio-Process Systems Alliances/SOCMA (BPSA) (Washington, D.C.)
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- California Life Sciences Association (CLSA) (San Francisco, CA)
- Colorado BioScience Association (Denver, CO)
- D2L Pharma (Bangalore, India)
- Massachusetts Biotechnology Council (Cambridge, MA)
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- San Diego Biotechnology Network (SDBN) (San Diego, CA)
- Washington Biotechnology & Biomedical Association (WBBA) (Seattle, WA)

To ensure global coverage for this project, we again invited major ***Media Sponsors*** to support our outreach to biopharmaceutical decision-makers. Our media sponsors, who helped ensure broad and representative coverage of industry participation, include:

- American Pharmaceutical Review (South San Francisco, CA)
- BioCompare (South San Francisco, CA)
- BioPharm International (Iselin, NJ)
- BioProcess International, (Westborough, MA)
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The early participation of our authors and sponsors in evaluating the areas and trends to be surveyed this year ensured the project was designed to cover the most relevant issues in biopharmaceutical manufacturing today. As always, their continued support was critical to the success of the project.

Eric S. Langer
Editor

ABOUT BIOPLAN ASSOCIATES, INC.

BioPlan Associates, Inc. is a biotechnology and life sciences market analysis, research, and publishing organization. We have managed biotechnology, biopharmaceutical, diagnostic, and life sciences research projects for companies of all sizes for almost 30 years. Our extensive market analysis, research and management project experience covers biotechnology and biopharmaceutical manufacturing, vaccine and therapeutic development, contract research services, diagnostics, devices, biotechnology supply, physician office labs and hospital laboratory environments.

We prepare custom studies, and provide public information our clients require to make informed strategic decisions, define objectives, and identify customer needs. With market information, our clients are better able to make informed, market-based decisions because they understand the trends and needs in high technology industries.

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Mr. Ronald A. Rader has written and edited dozens of books and studies on biotechnology topics. He created the first biosimilars pipeline database, and is qualified with a B.S. (Microbiology), M.L.S. (Library Science). He has over 35 years' experience as a biotechnology, pharmaceutical and chemical information specialist and publisher. From 1988-2003, he was Editor/Publisher of the Antiviral Agents Bulletin, the only periodical specializing in antiviral/HIV drug and vaccine development. In 1994, he published the Federal Bio-Technology Transfer Directory, abstracting and indexing all federal laboratory, e.g., NIH, inventions and technology transfers in biotech/biomedical areas, further marketed as an online database until 2000. Mr. Rader published BIOPHARMA: Biopharmaceutical Products in the U.S. and European Markets starting in April 2001, now www.biopharma.com. Mr. Rader has also been Manager of Information Services, Porton International plc, then the largest privately-held biotech company. Prior to that he served as a biomedical/chemical information specialist/manager/analyst with companies including Gillette Medical Evaluation Labs., Gillette Co.; MITRE Corp.; Biospherics; Computer Sciences Corp. (CSC); Technical Resources Inc.; and Bio-Conversion Labs.

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Amit Dua is the Global Marketing Strategy Leader for GE Healthcare Life Sciences Bioprocess business. Amit's primary focus is to align Bioprocess market insights with technology trends to drive value added initiatives for the biopharmaceutical industry. Amit has been in the Life Sciences industry for 11 years and has held multiple commercial roles in sales, marketing and product management. He also participates in several industry groups such as BioProcess Systems Alliance (BPSA) and International Society of Pharmaceutical Engineers (ISPE) and serves on the Advisory Board for Biopharma Asia and BPI East/West. Amit holds a BS in Bioengineering from Stonybrook University and MBA from Columbia Business School.

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Mr. Galliher earned his BA in Biology at Boston University (1975) and MS degree in Biochemical Engineering at MIT (1981) after which he held technical management positions at Biogen, Inc., Alpha-Beta Technology, LeukoSite, and Millennium Pharmaceuticals. Mr. Galliher helped lead teams who developed scalable bioprocesses, build facilities, and achieve commercial licensure of Avonex™ (beta-interferon) and CAMPATH™ monoclonal antibody. In 2002 he became Founder, President and CEO of Xcellerex, a single use technology/services company, acquired by GE Healthcare in 2012 at which he continues as Chief Technology Officer, Upstream. In 2012 Mr. Galliher was awarded Bioprocess International's 2012 "Thought Leader of the Decade, Upstream". Mr. Galliher is committed to the potential of biotechnology to transform human health, and is a co-inventor of numerous patented inventions in the field of advanced, high efficiency biomanufacturing technologies.

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Morten Munk is bio-pharmaceutical technology expert with 30 years of experience in the industry in Asia, South America, USA and Europe. Morten is Global Technology Partner at NNE, a pharmaceutical engineering company, where he advises on best technologies for effective pharmaceutical development and manufacturing as well as other aspects concerning compliant pharmaceutical engineering. From 2007 to December 2014, Morten was Vice President of Business Development at CMC Biologics, a global Contract Manufacturing Organization (CMO) with bio-manufacturing facilities in Europe and the USA. In this position he oversaw business development and negotiated several million Euro commercial supply agreements. Earlier, Morten was Vice President at CMC Biologics, heading the downstream operations division. Prior to founding CMC Biologics in 2001, Morten held a position as principal scientist at Novo Nordisk A/S where he was responsible for the CMC part of several projects, which have been commercialized successfully. Moreover, Morten writes technical, quality-oriented articles and technical reports, and organizing international conferences.

Kent Payne, CEO, Socorro Pharmaceuticals

Dr. Payne has extensive executive experience running start-up and growth businesses within both Fortune 500 as well as Private Equity environments. He combines strong business leadership, successful P&L track record, and technical background to strategically lead and grow enterprise value across biotechnology and pharmaceutical market segments. He has successfully led the geographic expansion of businesses into Europe, Asia and South America. Dr. Payne is currently President and CEO of Socorro Pharmaceuticals, a generic pharmaceutical company. He previously was President of the Americas for Qualicaps, Inc. (a wholly-owned subsidiary of Mitsubishi Chemical Holdings). He was a co-founder and partner of Asklepios Capital LLC, an angel investment company focused on advancing biotechnology and life sciences and providing executive/board advisory services to emerging biotechnology companies, and he was a Principle Consultant and Partner at CoreFactor LLC, providing executive, strategic, licensing, and operational advisory services to clients. He also previously held executive leadership positions of

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Dr. Stefan R. Schmidt currently serves as Chief Scientific Officer at Rentschler Biopharma SE, a leading CDMO, focusing on innovation and new technologies. Previously he was responsible for process science and production there and held various senior management positions at other international Pharma and Biotech Corporations like AstraZeneca in Sweden or ERA Biotech in Spain. He started his industrial career more than 20 years ago at the German hotspot of Biotechnology in Martinsried. During his academic education he earned a PhD in Biochemistry from the Julius Maximilians University in Würzburg, Germany and an MBA in Marketing from the University of Gävle in Sweden. In the last 10 years he worked intensively with fusion proteins, resulting in editing and authoring the first comprehensive book on that topic.

Joseph Shultz, Head of Advanced Process and Manufacturing Technologies, Novartis Pharma AG

Joseph Shultz is the Head of Advanced Process and Manufacturing Technologies at Novartis Pharma AG. His more than 25 years in the industry spans Development, Manufacturing, Quality and technology development. He has held influential positions at the Novartis, the Battelle Memorial Institute and Amgen, Inc., where he helped to initiate the technologies and strategies that became Amgen's Next Generation Manufacturing biomanufacturing plant.

Christoph Winterhalter, Senior Vice President, Business Development, AGC Biologics

With an educational background as microbiologist with Ph.D. from the Technical University in Munich in 1995, Christoph Winterhalter's career started as head of a genetic fermentation lab with metabolic engineering of E. coli developing the first route to fermentation based cysteine at Wacker Chemie AG, continued with commercializing the successfully patented cysteine process as Senior Project Manager, heading 2 global business teams with products and services in Pharmaceuticals / Nutraceuticals / Confectionary in Director roles, then heading the Division Biosolutions Americas locally at Wacker Chemical Corporation during a 3 years stay in US as Vice President Biosolutions till 2013. After returning to Germany he was heading the Business Development & Sales at Rentschler Biotechnologie GmbH in the biopharmaceutical contract development and manufacturing market (CDMO). After 4 years during which sales tripled and capacity doubled at Rentschler Biotechnologie GmbH, he is now the Senior Vice President Business Development at AGC Biologics, a global CDMO player with 6 sites in US, EU and Japan.

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METHODOLOGY

This report is the fifteenth in our annual evaluations of the state of the biopharmaceutical manufacturing industry. The strength of this study's methodology remains in its breadth of coverage, which yields a composite view from the respondents closest to the industry. This year, BioPlan Associates, Inc. surveyed 222 qualified and responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations in 22 countries; plus 130 industry vendors and direct suppliers of materials, services and equipment to this industry segment. Using a web-based survey tool, we obtained and evaluated information regarding respondents' current capacity, production, novel technology adoption, human resources, quality, and outsourcing issues. We assessed respondents' projected reasons for bottlenecks, and their perception of how these bottlenecks might be resolved.

We continue to provide additional in-depth analysis of specific issues affecting the industry in Chapter 2. These Monographs cover the events shaping the past year, and evaluate how they will affect, or create trends that will shape biopharmaceutical manufacturing over the next five years. We also have included this year a chapter on Fill-and Finish operations. Over the past few years, advances in technologies, drug delivery, and single-use applications have increasingly made this segment an area of interest for innovation.

To ensure comprehensive global coverage, we partnered with world-wide organizations to ensure the most accurate overview of the worldwide biopharmaceutical industry. Our industry partners are included in our acknowledgment section. In addition, to support this coverage, we also include acknowledgment of our media partners, whose assistance enabled us to reach the high quality of respondents required in this quantitative analysis.

Further information on methodology, breakouts on specific segments, and data from earlier surveys may be obtained by contacting us at the address below.

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CHAPTER 0: DEMOGRAPHICS

INTRODUCTION

Survey respondents included diverse biopharmaceutical senior managers, executives and scientists covering a spectrum involved in biopharmaceutical development and manufacturing, including those within CMOs. As reported below, ≥92% of respondents had VP, CEO or Director job titles. In addition, in Chapter 13, we separately present responses from bioprocessing suppliers and vendors. As in previous years, responses are from companies of all sizes and types. Respondents have a broad range of responsibilities, but all respondents had to qualify as involved with bioprocessing/manufacturing in some way.

This is an international project done annually, with this now the 15th year edition. We solicit and receive survey responses from individuals at organizations around the world. This year includes input from individuals based in 22 countries.

The diversity of survey respondents supports providing a comprehensive view of the industry from those most involved in managing biopharmaceutical manufacturing activities worldwide. Resulting survey data offer a means for understanding the industry and its future course. The breakdown of results by organization class, such as into CMOs vs. biotherapeutic manufacturers, provides further insights into these two major segments of the industry. These two types of organizations have different business drivers, risk profiles, costs of capital, etc.

0-1 RESPONDENTS' AREA OF INVOLVEMENT

Of the 222 biopharmaceutical manufacturers' and contract manufacturing organizations' (CMOs) staff responding to this year's survey, 27% were primarily involved in *"Process Development for biopharmaceutical manufacturing",* up from 25.6% in 2017 and 27.0% in 2016. 23.4% were involved in *"Large-scale cell culture production for therapeutics",* a slight decrease from 25.1% in 2017, 23.0% and 23.6% from 2016 and 2015, respectively. A slight increase to 15.8% from 14.1% in 2017 was seen in those involved in *"Scale-up (or clinical-scale) production for biopharmaceuticals PRIMARILY"* compared with 12.6% in 2016. But overall, the general pattern of type of organization of those surveyed has not changed.

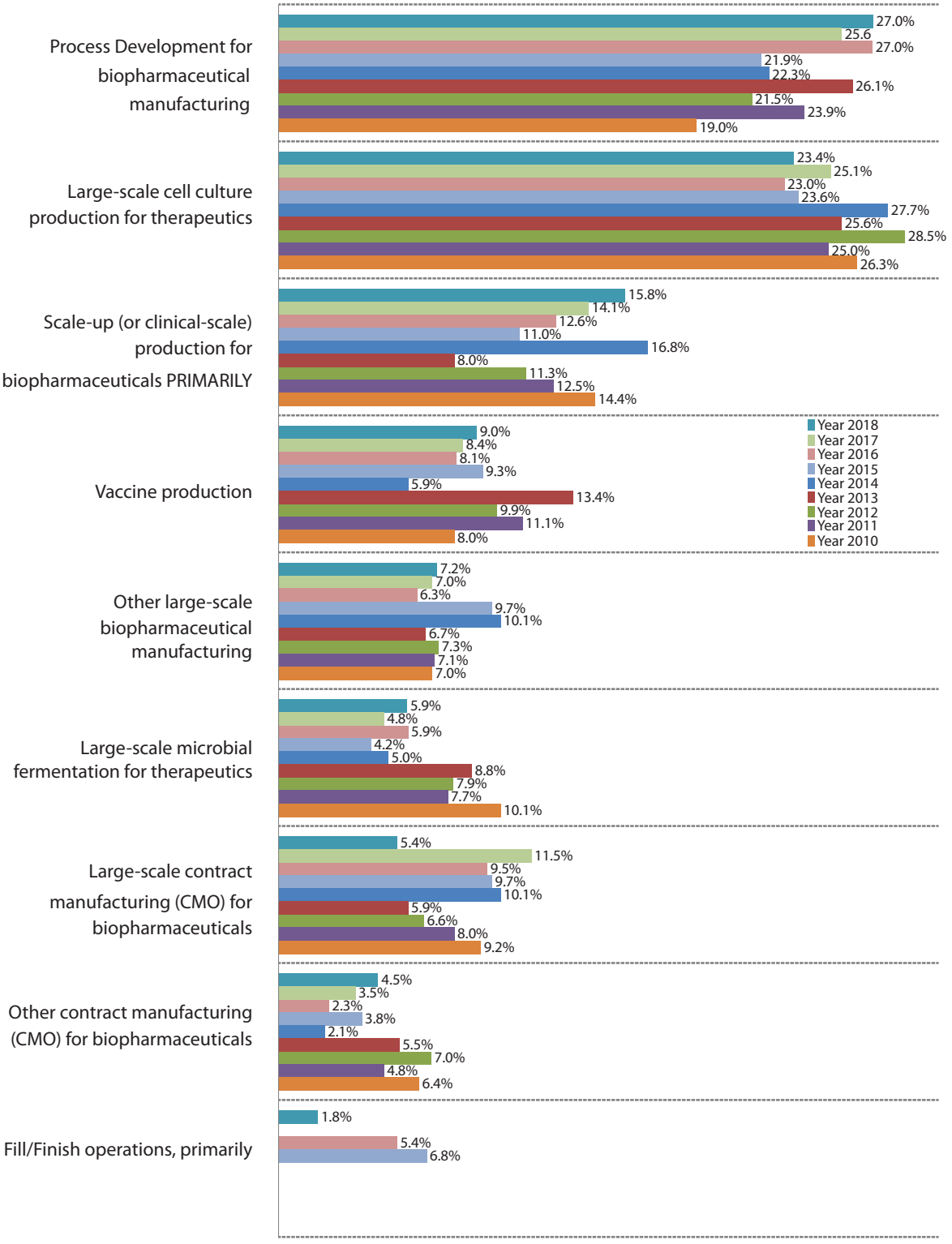
Respondents involved with *"Large-scale contract manufacturing (CMO) for biopharmaceuticals"* sharply dropped to 5.4% from 11.5% in 2017 and 9.5% in 2016. *"Large-scale microbial fermentation for therapeutics"* accounted for 5.9% of respondents, an increase of 1.1% percentage point; and 9.0 % of respondents indicated they were primarily involved in *"Vaccine production",* a slight uptick from 8.4% in 2017 and 2016 (8.1%). *"'Other' large-scale biopharmaceutical manufacturing"* respondents accounted for 7.2% of the total in 2018, an

increase from 7.0 in 2017 and 6.3% in 2016, and *"'Other' contract manufacturing (CMO) for biopharmaceuticals"* accounted for 4.5% of respondents, back up to 2015 levels (3.8%). Lastly, 1.8% of respondents accounted for *"Fill/Finish operations",* a sharp decline from 5.4% in 2016.

Overall, the makeup of respondents remains overall consistent with prior years' studies. Despite variations, including decreases, in reporting involvement in aspects of biopharmaceutical manufacturing, this year's data continues to fall within the range generally defined by prior years' data reporting, with the relative rankings remaining largely unaffected. This year-to-year coherency supports the accuracy of these demographic data.

Fig 0.1: Area of Primary Involvement in Biopharmaceutical Manufacturing, 2010 to 2018

"In which area of biopharmaceutical manufacturing is your organization currently involved?" (2010 to 2018)

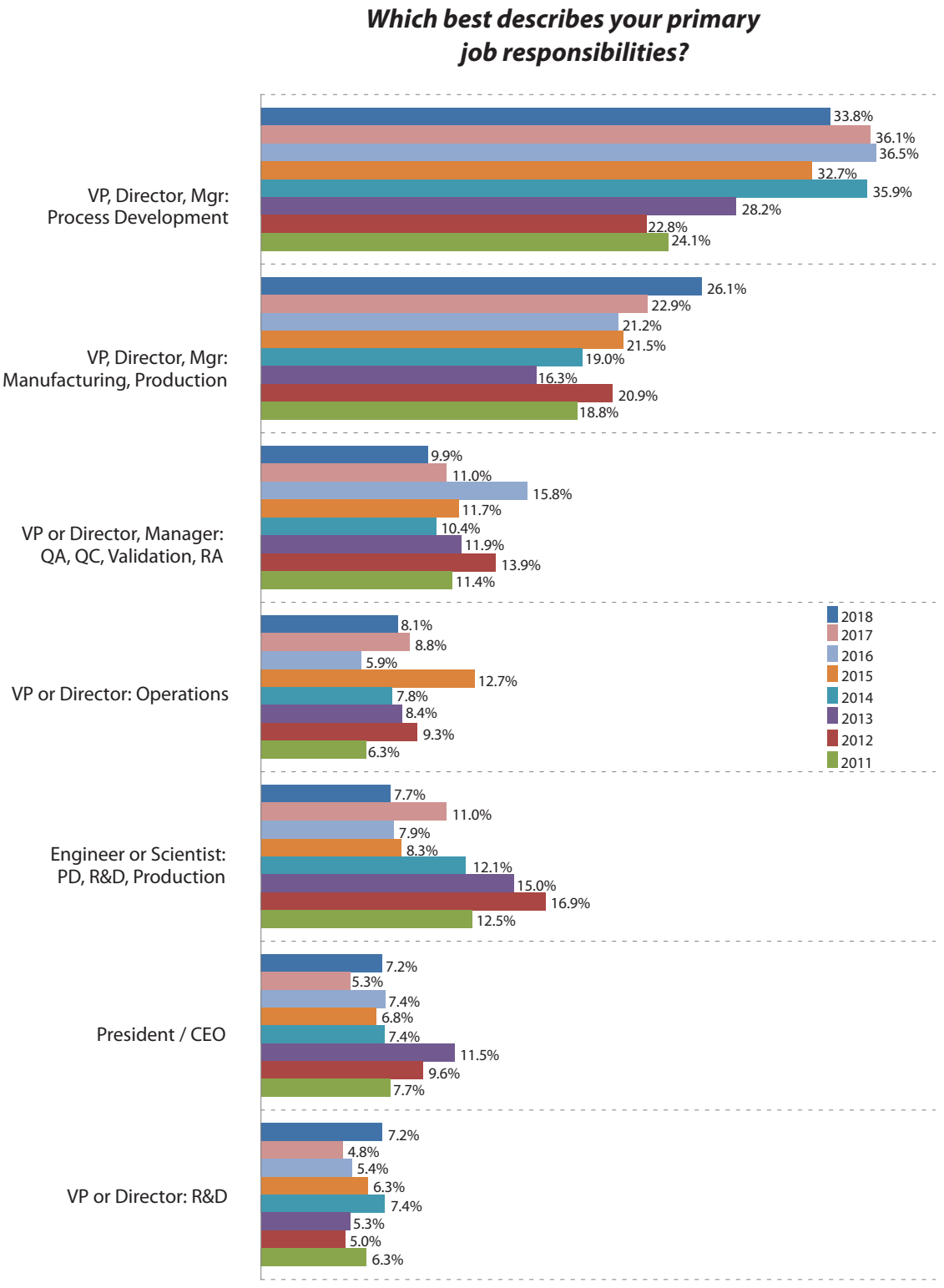


0-2 RESPONDENTS QUALIFICATIONS

Respondents were asked about their areas of responsibility, as indicated by job titles (Fig 0.2). Over 92% had titles of *VP, Director or President/CEO,* an increase from last year's 88%, but still consistent with 92% in 2016, 91.7% in 2015 and nearly 88% in 2014, with about 90% being the average in recent years. This year, only 9.9% of respondents were *VPs, Directors or Managers of QA, QC, Validation, or RA,* a decline from 11.0% in 2017 and a high of 15.8% reported in 2016. *Biopharmaceutical Scientist or Engineer* respondents lacking VP/Director/Manager responsibilities in Process Development, R&D or Production made up 7.7%, a decrease from 11.0% in 2017, 7.9% in 2016, and 8.3% in 2015.

Presidents/CEOs represented 7.2% of respondents, an increase from 5.3% in 2017 and 7.4% in 2016; and *VPs or Directors of R&D* accounted for 7.2% of respondents; still averaging similar totals seen in past years. Respondents with *VP or Director: Operations* responsibilities decreased slightly to 8.1% from 8.8%, and 5.9% in 2016. *VPs, Directors or Managers in Process Development* comprised the largest percentage of respondents at 33.8% down from 36.1% and 36.5% reported in 2016. *VPs, Directors or Managers of Manufacturing and Production* comprised the second-highest number of respondents at 26.1% over 22.9% in 2017. Combining *VPs with Process Development Directors and Managers* with those in *Manufacturing and Production,* the percentage comes to 59.9%, making up most of the respondents. Overall, respondent job titles or levels of responsibility have changed little over the years.

Fig 0.2: Respondents' Job Responsibilities, 2011 – 2018

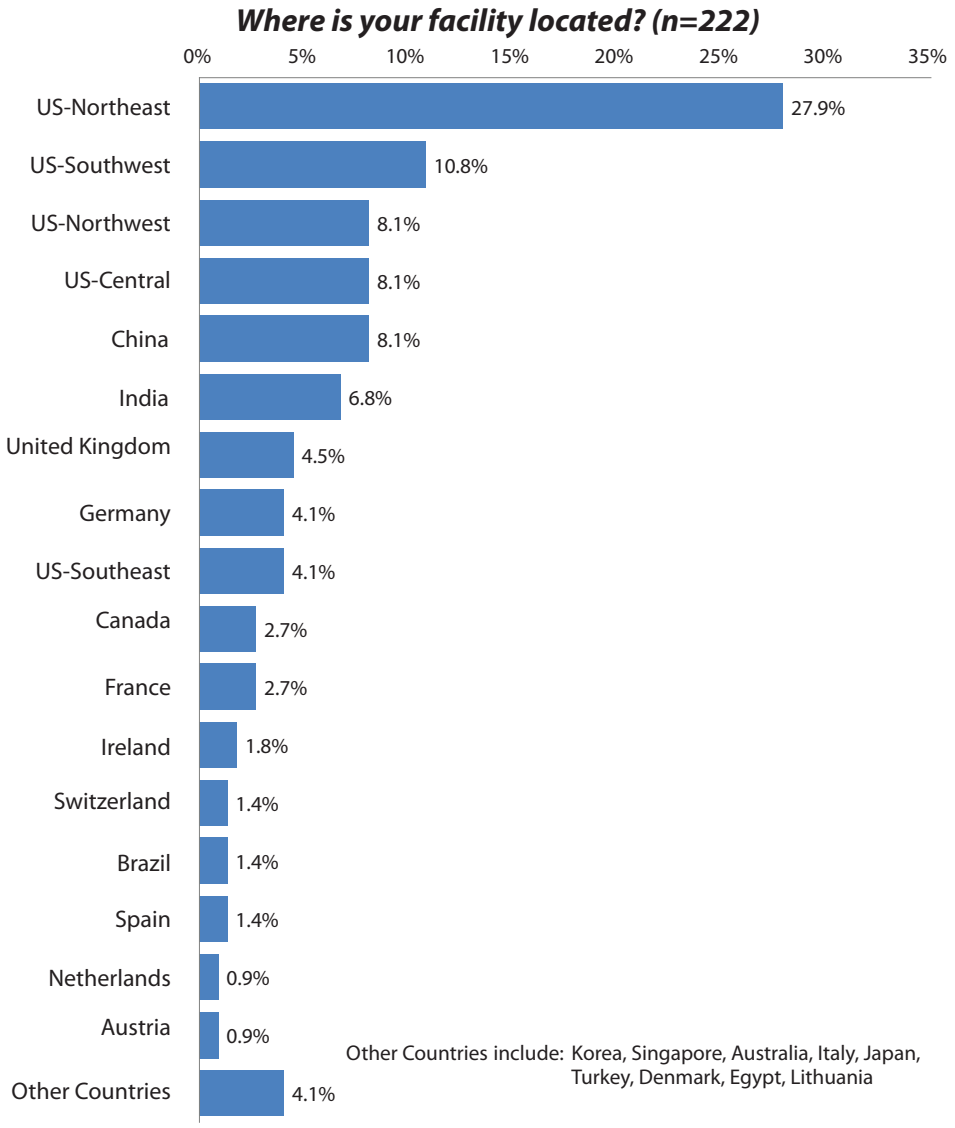


0-3 FACILITY LOCATIONS

This year surveyed respondents were based in 22 countries. Approximately 59% of the respondents were from the United States, with the Northeastern U.S. continuing to make up the largest group of respondents in the U.S., at 27.9%, a slight increase from 28.6% in 2017. Respondents from Western Europe made up 18.9% of the total, a decrease from 24% in 2017, 21.4% in 2016 and 19.7% in 2015. Asia is well-represented, including 6.8% from India and 8.1% from China. Other countries (the "Rest of World" not covered by reporting of specific countries) made up 21.6% of the respondents. Most of these are in European countries not specifically listed. The country geographic distribution of respondents is similar to the distribution of bioprocessing facility capacity, discussed in sections below.

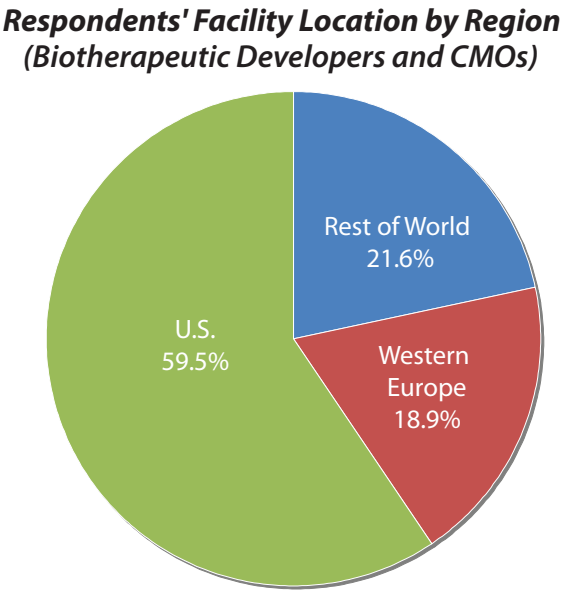
Further information about biopharmaceutical manufacturing facilities worldwide is available at the *Top 1000 Global Biopharmaceutical Facilities Index Web site* from BioPlan Associates (www.Top1000Bio.com).

Fig 0.3: Facility Location



We note that there was an increase in U.S. respondents (59%), up from 54.9% in 2017 and 61.2% in 2016, which returned to the level of participation prior to the decline in 2017. Western European responses saw a decrease from 24.0% in 2017 to 18.9% in 2018, closer to the near constant 20% participation since 2011. This year 'ROW' responses rose again to 21.6%, over 20.7% in 2017, closing the gap in the peak experienced of 22.0% in 2013.

Fig 0.4: Facility Location, by Region



Western Europe respondents include: *Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, Switzerland, United Kingdom, Holland, Hungary, Norway and Turkey.*

"Rest of World" respondents include: *Canada, Australia, India, China, Singapore, Egypt, Japan, Russia, Estonia, Iceland, Israel, Argentina, Brazil, Bulgaria, Cuba, Korea, Lithuania, New Zealand, Poland, Slovenia, South Africa, Taiwan, Malaysia, Iran, Mexico, Albania, Philippines, Vietnam, Pakistan, Chile, Indonesia and Puerto Rico.*

0-4 AREAS OF BIOPHARMACEUTICAL MANUFACTURING OPERATIONS

Mammalian Cell culture continues to dominate product development and manufacture, and this is reflected in the survey data. Further, a majority of biopharmaceutical products in the development pipeline and entering the market are mammalian-expressed, including various recombinant monoclonal antibody (mAb) products, with this now including multiple biosimilar versions of many of these mAbs. With the continuing incremental increases in mammalian system titers and yields, and with mammalian culture all that many bioprocessing professionals are now knowledgeable about, many facilities are standardizing using mammalian vs. microbial systems. In some cases, this even includes products that could be manufactured in microbial systems, which are generally cheaper or more productive, but are now often initially manufactured in mammalian systems, if these get the job done, such as to produce pre-clinical or early clinical supplies. Besides mammalian being the dominant platform, but generally more expensive than microbial manufacture, technology development continues using mammalian platforms. Mammalian manufacturing has advantages including being more adaptable to single-use systems manufacturing, besides more bioprocessing professionals now being more familiar with mammalian vs. microbial manufacturing. The state of mammalian and microbial manufacturing is also discussed in other sections below.

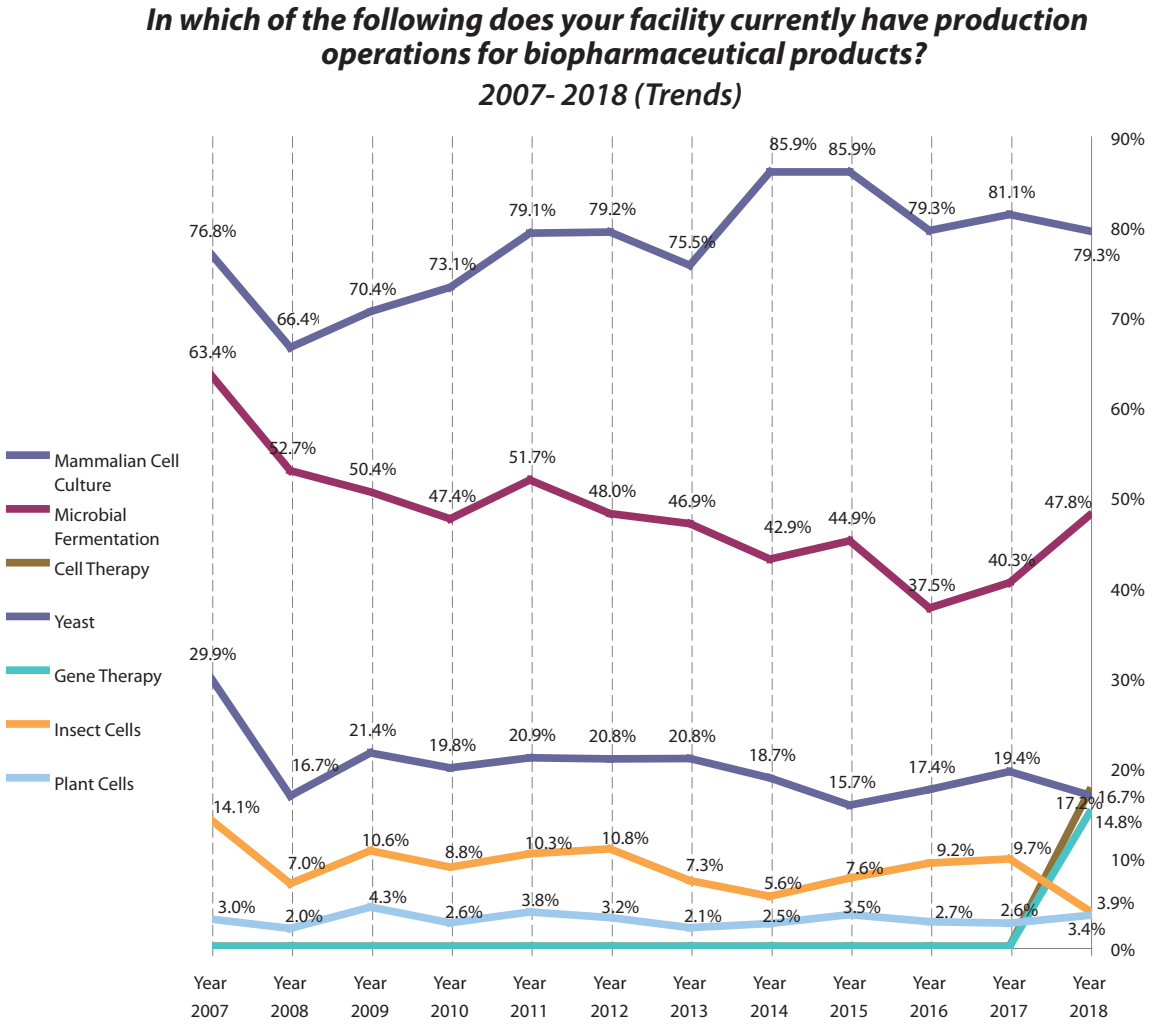
Respondents reported involvement in seven categories of expression systems for 2018. Percentages ranged from 79.3% *(Mammalian Cell Culture)* to 3.4% *(Plant Cells).*

This year, we see a decrease from 2017 in those reporting their facilities using *Mammalian Cell Culture* (81.1% to 79.3%); and an increase in *Microbial Fermentation* systems again, where 47.8% of respondents noted facility involvement in this area, a 7.5%-point increase over 2017 (40.3%).

Also observed were decreases in the overall percentage of respondents for *Yeast,* from 19.4% to 16.7% in 2018, 1% above the drop in 2015; and *Insect Cells,* a 5.8% drop from 2017 to 3.9% in 2018. Note: respondents were permitted to select multiple platform systems.

Relative to 2017, *Microbial Fermentation, Cell Therapy* and *Gene Therapy* reported steeper increases in 2018. *Plant Cells* showed only a slight increase over 2017 (2.6% to 3.4%, less than 1% above the 5-year average. industry appears to be slowly if at all, increasing the diversity of basic expression systems/platforms it is using.

Fig 0.5: Biopharmaceutical Manufacturing Systems, (2007-2018) Trends



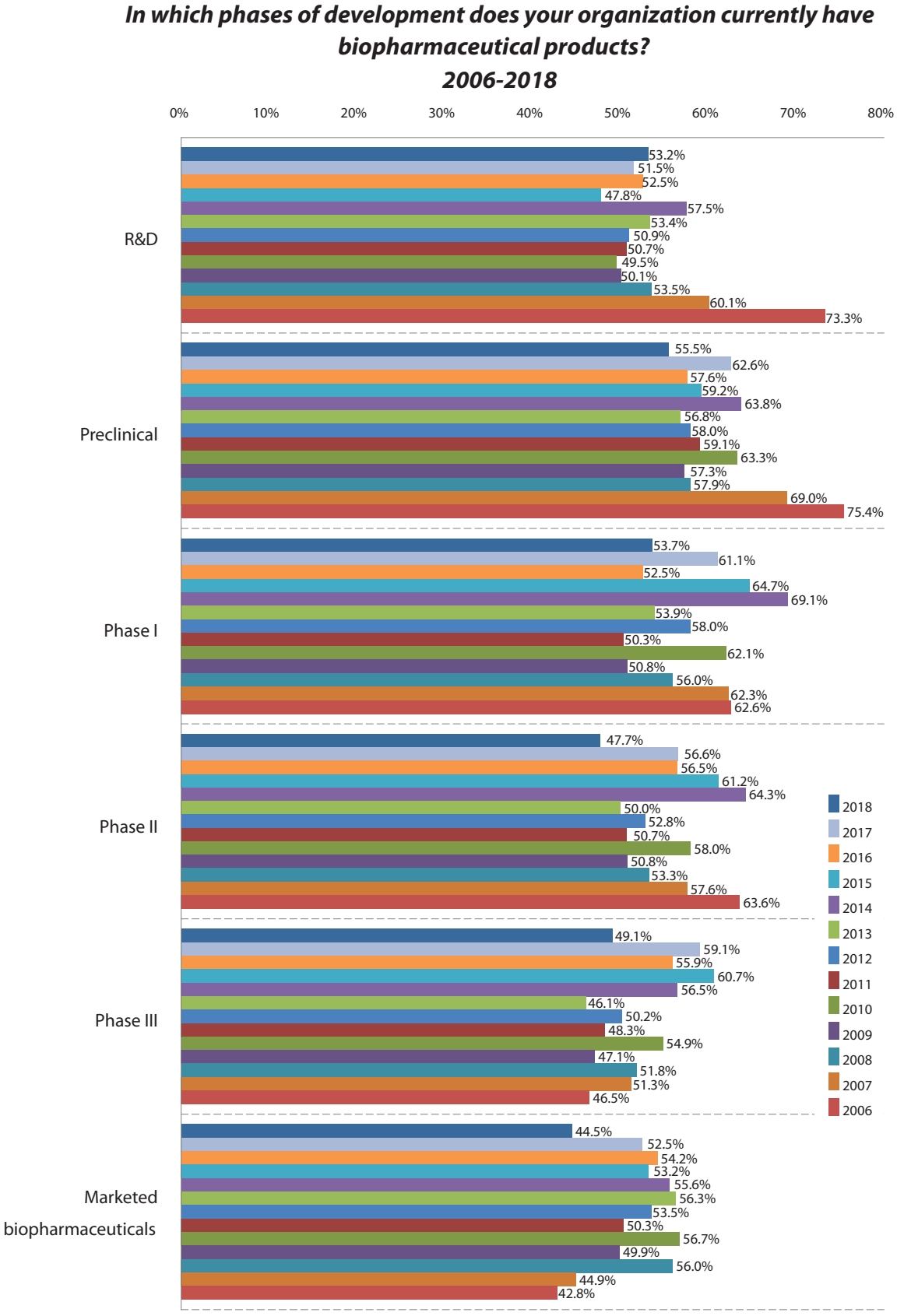
0-5 PRODUCTION OPERATIONS, PHASE OF DEVELOPMENT

Wei dentified the phases of pipeline development in which respondents' organizations (companies) had products. This year, over half (53.2%) of respondent companies had products at R&D stage, an increase of 1.7% over 2017 (51.5%). Respondents' facilities involved with R&D have shifted back to their relative 50% level seen in almost all previous years, but they remain much lower than the 73.3% in 2006. Respondents reporting their facilities involved with Preclinical operations were 55.5%, a decrease over last year's 62.6%. Note: respondents could indicate multiple phases of development for their facility.

The percentage of respondents whose facilities have biopharmaceutical products on the market decreased again to 44.5%, down from 52.5% in 2017. Those working with Phase I development saw a drop from 61.1% in 2017 to 53.7%. However, the largest change seen in any of these categories are those facilities involved with products in Phase III development, which dropped to 49.1%, down 10% from 2017. Perhaps, this suggests a recent tightening of company development pipelines. Hopefully, developers are making better choice regarding their product candidates, including failing faster and/or less frequently.

The respondent facility phase of development data continue to have small annual fluctuations as the industry continues its overall maturation, with most respondents now employed by companies with revenue streams from marketed biologics. 2009 has been widely noted as the year the biopharmaceutical industry finally, as a whole, turned a profit. Overall, the employers of the surveyed biopharmaceutical manufacturing-related professionals are rather evenly distributed over the pipeline spectrum from pre-clinical through commercial manufacturing, with each phase being worked on by 50+% of survey respondent organizations.

Fig 0.6: Phase of Development of Surveyed Respondents, 2006-2018

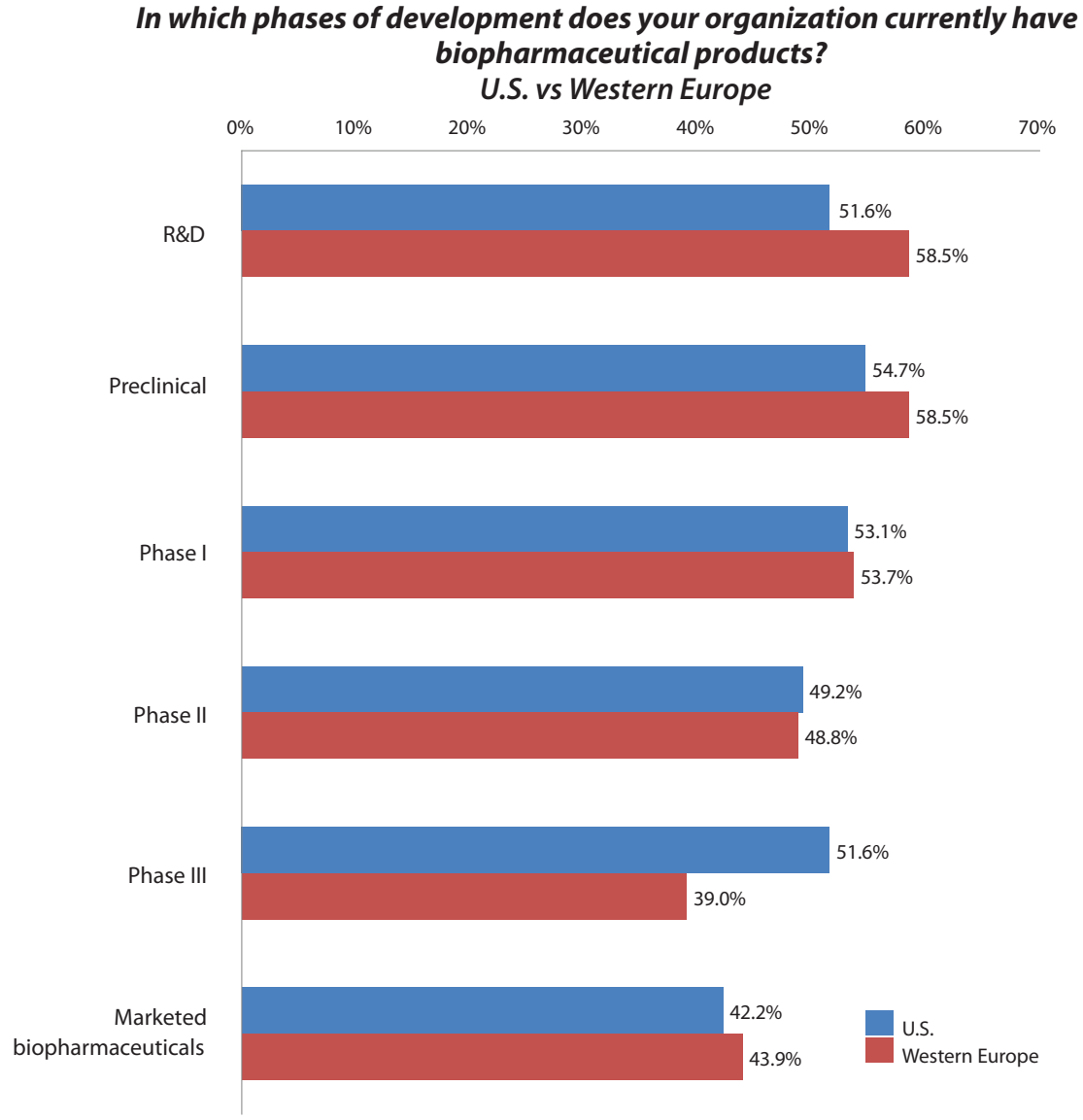


Western European respondents indicated a higher involvement by their companies with *Preclinical* products, while U.S. companies indicated a lower involvement at 58.5% vs. 54.7%, respectively. In 2017, Western European respondents indicated a lower involvement than U.S. companies (55.3% vs. 66.1%) respectively. This is a shift and reversal of last year's findings.

In 2018, we see U.S. and Western European facility respondents report almost the same percentage of *Phase I* clinical trials (53.1% vs. 53.7%, respectively). Contrast that to 2017, where the U.S. clinical trials were much higher than W.E. with 65.1% vs. 55.3%, respectively. Another trend seen this year is a large increase in U.S. *Phase III* clinical trials vs. Western Europe, (51.6% vs. 39.0%), a large decrease for W.E. from 2017 (60.6% vs. 55.3% W.E.) and decrease from 2015 (71.8% W.E.).

European and U.S. respondents involved in commercial products dropped from 51.1% vs. 49.5% in 2017, respectively, to 43.9% and 42.2% in 2018, respectively.

Fig 0.7: Phase of Development of Surveyed Respondents, (U.S. vs Western Europe)

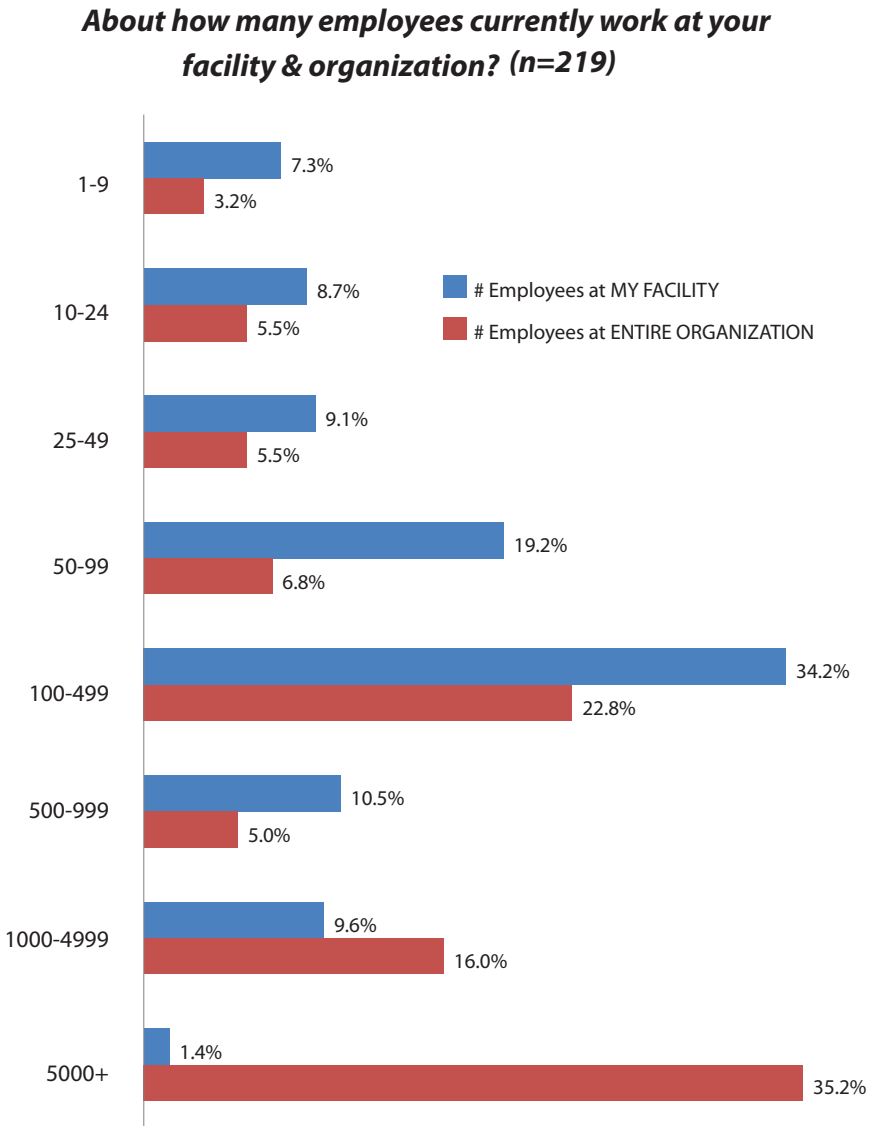


0-6 EMPLOYEES AT FACILITY

To evaluate issues such as capacity, single-use systems usage and other factors, we asked respondents to report the estimated number of staff within their own facility, and within their total organization.

The largest percentage of respondents continued to be at facilities with 100-499 staff. Continuing a prior trend, the largest share of respondents, 35.2%, were from parent organizations with greater than 5,000 employees, with as fully expected, most respondents presumably employed by Big (Bio)Pharma companies. These data reflect the relative distribution of biopharmaceutical manufacturing-related professionals' employment within the biopharmaceutical industry. This includes the increasing involvement and even dominance of larger companies in biopharmaceutical R&D and products marketing. And with most Big Pharma type companies and larger generic drug and foreign pharmaceutical companies continuing to move into biopharmaceuticals, the dominance of large companies as employers of biopharmaceutical manufacturing professionals will likely continue to incrementally increase.

Fig 0.8: Distribution of Employees at Facility, and Organization



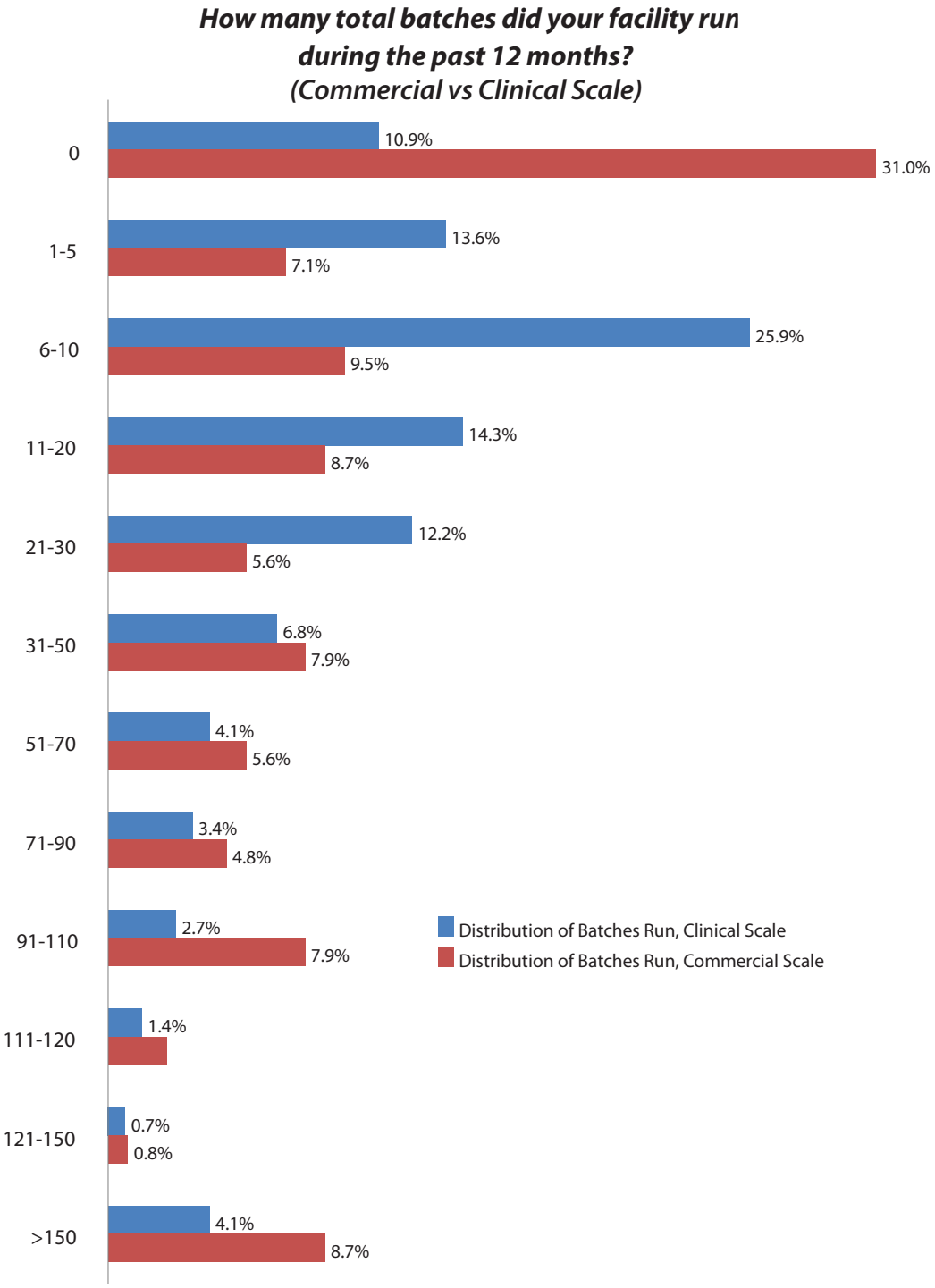
0-7 BATCHES RUN AT FACILITY PER YEAR

To continue our evaluation of issues such as batch failure rates, and to ensure we are capturing organizations involved in significant manufacturing processes at various scales of manufacture, we again this year asked for estimates of the number of batches or production runs at the respondent's facility (not the organization) over the past 12 months.

We found that for *'Clinical Scale'* manufacturing, about half of the facilities reported producing between 1 and 20 batches per year (53.8%), more than a 3% increase over 50.4% in 2017. At the *'Commercial Scale',* only 8.7% reported producing over 150 batches per year, down from 11.7% in 2017. Most among those manufacturing reported running between 0-70 batches per year (75.4%), compared to 75.9% last year.

To compare consistency of respondents' operations, year-by-year, we evaluated the number of batches run/year. This year (asking about 2018), we found between 0-10 batches at *'Clinical Scale'* were run by 50.4%, a 5.9% increase from 2017, and 47.6% were at *'Commercial Scale',* a 4.9% decrease from 2017. So, approximately half of respondents remain operating with no, or a lower number of production runs for Clinical and Commercial manufacturing.

Fig 0.9: Distribution of Total Batches Run at Facility Last Year, by Scale of Production



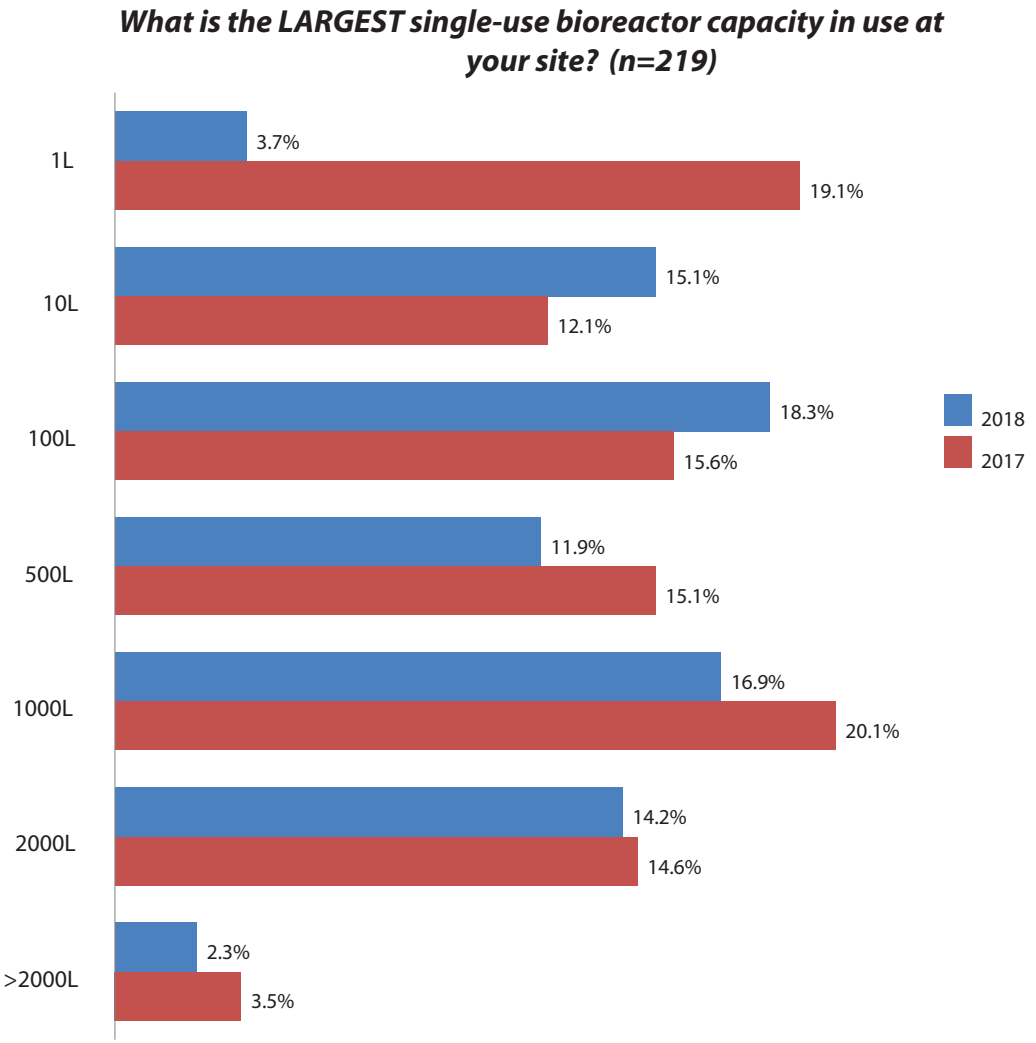
0-8 SINGLE USE BIOREACTOR CAPACITY, IN USE AT SITE

To follow the trend of single-use bioreactor capacity within the industry, we asked respondents again this year what the largest single-use bioreactor capacity in Liters was in use at their site.

The highest percentage response increase for 2018 was 100 L capacity, increasing to 18.3% of respondents. A total of 16.9% of respondents noted their largest single-use bioreactor capacity was 1000 L, indicating the respondent is likely at a late-stage clinical or even commercial manufacturing facility. The next highest percentages were for 10 L and 2000 L, with 15.1% and 14.2% responding, respectively.

Over 1/3rd, 33.4%, reported their facility as having ≥1,000 L single-use bioreactors, i.e., working at large-scale by single-use standards. As expected, very few respondent facilities, 2.3%, had single-use bioreactors with greater than 2,000 L capacity. However, this percentage is expected to incrementally increase in coming years.

Fig 0.10: Distribution of Largest SINGLE-USE Bioreactor Capacity



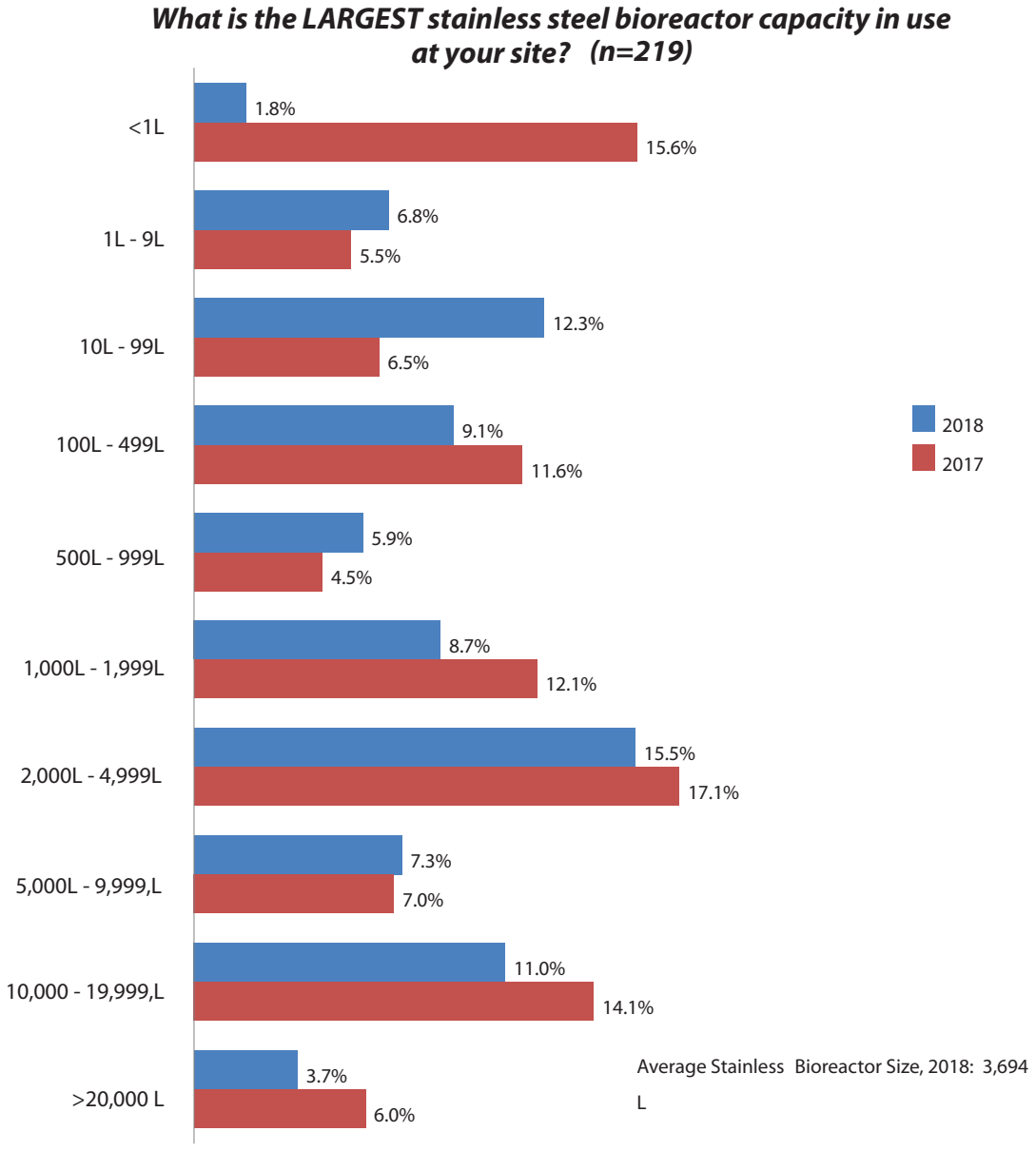
0-9 STAINLESS STEEL BIOREACTOR CAPACITY, IN USE AT SITE

We asked respondents again this year what was the capacity of the largest stainless-steel bioreactor at respondents' facilities.

The 2018 average reported largest size of on-site stainless steel bioreactors is 3,694 L. The compared with about 600 L being the average size single-use bioreactor at survey respondents' sites. The highest percentage, at 15.5%, reported 2,000-4,999 L at their facility. The next highest percentage reported bioreactors with less than 10 – 99 L of capacity at 12.3%, followed by 11.0% reporting 10,000-19,999 L. Respondents reporting their largest bioreactor as having less than 1,000 L capacity made up slightly less than half at 35.9%.

Comparing the data reported for facility largest single-use vs. stainless steel bioreactors, over 1/3rd (37.5%) of facilities with stainless steel have ≥2,000 L bioreactors vs. only 16.5% for single-use.

Fig 0.11: Distribution of Largest STAINLESS Bioreactor Capacity



CHAPTER 1: INTRODUCTION AND DISCUSSION

1-1 INTRODUCTION: THE PHARMACEUTICAL AND BIOPHARMACEUTICAL INDUSTRIES

The pharmaceutical and biopharmaceutical industries remain active, profitable and growing economic activities and industries, despite about a decade ago having recovered from worldwide economic problems, increasingly being targeted for criticism for excessively high prices, and biosimilars/biogenerics increasingly a threat to established products. There are estimated to be well over 10,000 therapeutics in R&D, both drugs (chemical substance pharmaceuticals) and biopharmaceuticals (biotechnology-derived pharmaceuticals), with nearly 40,000 ongoing (or recently reported) clinical trials. Among these, ≥40% or likely soon approaching 5,000 candidate products in R&D are biopharmaceutical products. A significant portion, >1,400, of products in the development pipeline are follow-on biopharmaceuticals, mostly biosimilars and biobetters in major markets and a large number of biogenerics in developing countries and international commerce.

The large number of biosimilars and biobetters in development indicate the maturation of the biopharmaceutical industry, as its current major blockbuster products start to go off-patent. This represents a considerable shift in the biopharmaceuticals' product mix, and a rapidly increasing number of marketed biopharmaceutical products from as short as 5 or more years ago. This large proportion of industry R&D and manufacturing being devoted to follow-ons also reflects a basic shift in the pharmaceutical industry from small molecule drugs to biopharmaceuticals.

Until relatively recently, pharmaceutical companies of all sizes, particularly the Big Pharma-type companies that now dominate biopharmaceutical R&D, have often continued to cut back on expenses as much as possible and consolidate R&D and companies, with the resulting companies often ending up concentrating on developing fewer products. Most every major merger/acquisition seems to include the acquirer up-front claiming the new company will have a larger and healthier pipeline products, increased capacity and expertise, etc. However, it also seems this rarely happens, with much merger/acquisition activity apparently more to just boost appearances and stock value, while the new bigger companies almost invariably soon consolidates cut-back their combined R&D pipelines, close facilities, outsource more tasks previously considered better done in-house, etc. As noted, luckily, this trend is slowing, although this could just be from there being fewer big-time players to support much additional merging and purging among these companies. But in terms of biopharmaceuticals, any such decreases in existing player company R&D is likely currently being more than counter-balanced by both other established pharmaceutical and new companies worldwide moving into biopharmaceuticals. This increasingly includes a large number of new entrants into the biosimilar/biogenerics, cellular and gene therapies areas.

But even if there were significant pipeline shrinkage, this may not be a negative trend. This could simply reflect the industry doing a better job in eliminating less promising candidates before they enter or earlier in clinical trials. This 'failing faster,' i.e., earlier in development, is generally less costly and disruptive than products failing later in development. If the industry is doing a better job of weeding out poor candidate products earlier, the industry may be on track for increased future success and increased productivity and profits, with fewer costly late-stage failures and a higher percentage of pipeline products making it to the market.

The pharmaceutical R&D pipeline and industry are becoming increasingly dependent on biopharmaceuticals. Besides profits, with biopharmaceuticals generally providing higher profits, this includes public image. Big Pharma companies, led by PhRMA, have been successful in their decade-plus efforts to co-opt the terms "biopharmaceuticals" and "biopharma," particularly in popular use, to include all pharmaceuticals, particularly all those that are innovative or otherwise have a positive public image [see Rader, R.A., "(Re)Defining Biopharmaceutical" Nature Biotechnology, July 2008, 26(7), p. 743-751]. Thus, it is now often a rarity when the 'biopharma' or 'biopharmaceutical' refers to biopharmaceuticals vs. innovative or all pharmaceuticals.

Biopharmaceutical products are being developed by an ever-increasing cross section of the pharmaceutical industry, including Big Pharma, generic drug and foreign companies, with many of these entering the field by developing biosimilars. These sources, along with smaller biotech business model-type biopharmaceutical developers, which have been the traditional source for most innovative biopharmaceuticals before licensing by larger companies, are continuing to expand the global biologics pipeline. Biosimilars, particularly, are bringing in many new biopharmaceutical developers and manufacturing facilities. This includes new entrants based in China, India and other developing countries increasingly entering biopharmaceutical R&D. An increasing number and percentage of new pharmaceuticals entering the market will be biopharmaceuticals vs. small molecule drugs; and these will originate from more diverse sources. Combine this with biopharmaceuticals (vs. drugs) generally costing much more and providing higher profit margins, and the pharmaceutical industry will increasingly be dependent on biopharmaceuticals for profits, innovation and its basic survival.

As biopharmaceuticals become an even more important part of the pharmaceutical industry and as many new players are entering the field and, as our annual survey shows, most every current manufacturing facility is expanding its bioprocessing capacity. Not only must bioprocessing output expand to handle manufacture of an increasing number of approved products and higher volumes as markets for many current products further expand, e.g., with approvals for new indications and growth in international markets, the industry must also be capable of handling a large number of pipeline products and related new products that continually enter the market. And the industry must also develop manufacturing capacity for a wide range of new(er) product types, e.g. cellular therapies, gene therapies, ADCs, stripped-down antibodies, RNAi, live microbes as therapeutics, etc.

The strategic importance of biopharmaceutical manufacturing and manufacturing capacity is increasing, and understanding the markets for biopharmaceuticals and bioprocessing technologies and services is becoming ever more important to those in the industry. Planning and decision-making concerning the manufacture of biopharmaceuticals are becoming more complex as companies continue, whether spurred by habit, actual need or for the sake of investors, to implement cost-saving efforts. This can include cutting back on the number of products in their development pipelines or outsourcing support and even critical tasks.

Effective planning within the (bio)pharmaceutical and bioprocessing markets is required to avoid problems later. This demands a high level of leadership, partnership, information sharing, and communication between manufacturers, CMOs and bioprocessing technology and equipment suppliers as they develop new manufacturing technologies, devices and capacity to keep pace with industry needs. Strategic production decisions must be based on solid bioprocessing and sales projection data, combined with a broad understanding of trends and effective benchmarking of capacity and production issues. This study provides an on-going evaluation of the vital manufacturing trends shaping this industry, and is designed to help keep those in the industry keep aware of the internal industry and external trends and issues affecting biopharmaceutical decision-making.

Companies, particularly larger and more established ones, are continuing to aggressively look for opportunities to cut costs and increase efficiency, with this continuing to benefit contract manufacturing and research organizations (CMOs and CROs). But many companies are increasingly confident and are pushing ahead doing full development and commercial manufacturing in-house. Prior rather common severe arbitrary cuts in staff and divestment of facilities have largely ended, but this may simply reflect already reaching the limits of eliminating in-house expertise and facilities.

Among many of the very largest companies, we still see cycles of short-term on-paper/ theoretical profits driving decisions and related investor concerns, with companies needing to distract investors from long-term problems, such as fewer products making it to the market, lower R&D productivity, payers resisting high-cost product coverage, etc., through habitual company merging and purging. This commonly includes merging or acquiring smaller (or just as large) companies and then consolidating, with staff lay-offs, closing of facilities, abandonment of products in the combined company pipelines, and other cut-backs. While involved companies typically claim synergies, that their resulting pipelines and finances will be better, that there will be more innovation, etc., this rarely happens, but the company survives and lives on, with investors happy for the moment. But as the consequences of mergers and acquisitions catch-up with the acquiring companies, they are then forced again to go through merge-purge cycles just to survive and please or distract investors. Many in industry seemingly have come to expect this as normal, how the mainstream major market-based pharmaceutical industry works, how these companies add to their valuations, etc.

A large portion of biopharmaceuticals coming to market involves treatment of ignored or currently untreatable indications, making them particularly welcome and needed. In recent years, this includes a large number of products for orphan indications, with FDA and other regulatory agencies proactively supporting this. This includes granting transferrable vouchers now selling for up to several $100 million each that grant the holder more rapid evaluation of product applications.

While much action in major market, affluent countries involves orphan therapeutics development, biogenerics directed to lesser-regulated international markets is where the growth is in developing countries. Many new entrant foreign companies of all sizes and types are developing biosimilars and/or biogenerics and plan to use these to establish themselves in the industry. This is resulting in a significant increase in the number of evaluation players and manufacturing facilities.

Most recent large commercial biopharmaceutical manufacturing capacity expansions have involved building fixed stainless steel bioreactor-based bioprocessing systems for commercial product manufacture. In the extreme, this is exemplified by Samsung and Celltrion in S. Korea. This is in contrast with production of supplies for R&D and clinical testing, which is now essentially dominated by use of single-use/ disposable bioreactor-based systems, with this

requiring much smaller bioreactors, facilities and infrastructure investment and construction. About the only area of bioprocessing not substantively using single-use systems at least for pre-commercial manufacturing is microbial fermentation, which generally uses much more extreme conditions (mixing, higher temperatures, etc.) than mammalian cell culture. We are early in a trend of developers adopting single-use systems for commercial product manufacturing, often involved scaling-out with multiple ≤2,000 L or even larger bioreactor-based process lines in parallel.

Recently there has been a significant increase in new single-use commercial-scale manufacturing facilities under construction and coming online. Most of these facilities are for biosimilars manufacture; and most are 'flexible,' able to be adapted for manufacture of multiple products (vs. being single product dedicated). These new single-use commercial manufacturing facilities include modular facilities, including the first good-sized modular bioprocessing facilities constructed in China.

Manufacturers must choose from an ever-increasing number and diversity of bioprocessing options. Besides classic make (manufacture in-house) vs. buy (outsource; use CMOs) decisions, this includes deciding among new and improved vs. legacy off-patent cell lines and genetic engineering/ expression systems technologies; bioprocessing systems, including new and improved single-use and stainless steel equipment; and outsourcing manufacturing to CMOs which are expanding their capacity, technologies, and service offerings. Increasingly, companies must make difficult and costly strategic decisions, including about commercial manufacture, earlier in product development.

A number of questions need to be answered and related decisions made by biopharmaceutical developers even before a product is shown effective in clinical trials. These include aspects such as:

- Should we use an older, off-patent expression system or a new, much higher yield, but more likely royalty-bearing system?
- Should we use single-use/disposable or fixed stainless steel bioprocessing equipment for clinical supplies manufacture?
- Which way should we go for commercial manufacturing – single-use or stainless steel? If we use single-use bioprocessing systems to support development, do we want to be among the pioneers to use single-use equipment for commercial manufacture or should we stick with familiar, trusted, but more expensive up-front, generally cheaper at largest scales, and labor-intensive fixed stainless steel equipment for commercial manufacture?

The biopharmaceutical industry survived last decade's worldwide economic downturn without being much affected in the long-term. In fact, the industry has done rather well for itself during what for most other industries was a recovery period – not contracting or losing much ground, rather continuing its growth with little interruption. The biopharmaceutical industry continues to remain dynamic, profitable and growing. This year, as in 2017 and prior years, survey results show that companies are spending and investing more on their R&D, new technologies, bioprocessing capacity, staff and other infrastructure. This is all fully expected, with as discussed below, biopharmaceutical revenue and profits continuing to increase.

Overall, 2018, like 2017 and other recent years, is fully expected to be a good year for the biopharmaceutical industry, with the industry remaining viable, relatively insulated from the worst of any major economic and political disruptions, even those that might be caused by the current U.S. administration, e.g., current threats of trade/tariff wars, and is well-positioned for solid future growth.

1-2 CURRENT STATUS AND MARKET TRENDS

The (bio)pharmaceutical industry is healthy and its financial status is continually improving. The world market for biopharmaceuticals is now over $250 billion and continues growing at a healthy rate. The world market for recombinant protein therapeutics is now ≥ $150 billion, with non-recombinant vaccines and blood/plasma products comprising nearly all the remainder. New products for new indications drive market growth in the major markets; and expanding markets, particularly internationally, continue to support overall market growth, but mostly with biosimilars/biogenerics.

The continued high growth rate in biopharmaceutical markets (revenue) will continue to drive investment in the industry, including at the expense of traditional small molecule drug development. With rather steady continuous growth, product development and manufacturing must continually increase to keep up. Biopharmaceuticals vs. drugs have simply proven themselves to be profitable investments, e.g., with much higher profits per sale and likelihood of attaining commercial success, including capturing market share, with this often simpler or more straightforward with innovative biopharmaceuticals. Also, since their cost of manufacture is generally much higher, biopharmaceuticals (vs. drugs) tend to be developed for diseases and indications generally lacking current good options for treatment, assuring them of eager markets upon launch (and also supporting high prices); and their sales prices are relatively high.

The reality continues that U.S. consumers (and tax-payers), in many respects, subsidize biopharmaceutical development and marketing for the rest of the world, with this evident in terms of innovative product development and the higher/highest prices for products in the U.S. market effectively subsidizing lower costs in other markets worldwide. So, if cost containment and/or price controls on biopharmaceuticals are ever substantively implemented in the U.S., costs will need to be increased in other markets. With the U.S. seen as benefiting considerably from its innovative biopharmaceuticals industry, this would likely be perceived as unfair in essentially all other countries. In the extreme, if faced with substantive U.S. price controls, the U.S. biopharmaceutical industry could adopt unitary, single worldwide pricing, with everyone paying much the same, with this resulting in price increases in most every country other than the U.S. However, doing this is politically very unlikely.

Some more specific trends and aspects of current biopharmaceutical markets status follows:

Cost-containment and Controls: The past year was noisier than recent prior years in the U.S. in terms of protests over exceedingly high pharmaceutical prices, and this trend will increase. Previously much or most attention was being directed not to biopharmaceutical products, but rather to a few expensive hepatitis C drugs, epinephrine auto-injectors, and some marketed drug (vs. biopharmaceutical) products where prices were drastically increased or launched at high prices. However, recent approvals and market launches, including cellular and gene therapy products at multiple 100s of $1,000s, is shifting attention to biopharmaceuticals, where it is likely to remain or increase as more of these start to enter the market. Many cite (or hope) the arrival of biosimilars in the U.S. and other major markets as likely to take some pressure off of calls for increased government cost containment and price controls in the U.S. and other major markets. However, biosimilars are a small niche, only affect relatively few fully mature products, and will not have substantial economic impact on U.S. healthcare spending for years to come. In the U.S. and many other markets worldwide, drugs for chronic hepatitis C and cancer and cellular/gene therapies that are curative but set records for costs are resulting in increased attention to pharmaceutical pricing practices. This includes politicians in the U.S. citing high prices and threatening un-informed reactive legislation. The U.S. remains the largest

market without significant government pharmaceutical price controls, including forced price negotiations for government health care institution purchases. However, this may change in the U.S. with its politics increasingly volatile and unpredictable. In many developed and affluent countries other than the U.S., such as India, cost containment and government-directed cost controls continue to adversely affect biopharmaceutical markets.

Adverse outcomes from price controls include their presence restricting developer company finances and innovative R&D, with investors viewing price controls as adversely affecting profits and companies avoiding product areas, indications, etc., where price controls are more likely to be encountered. This could be one of the factors contributing to a very large and still-growing portion of biopharmaceuticals in development being for orphan diseases/indications, where markets are small but needs, often for any effective therapeutic, are desperate. Gaining approval for a product much improved in efficacy and/or safety vs. existing products or simply being the first effective product for a serious or deadly indication essentially results in these products being priced based on a what-the-market-will-bear approach. That is, products are priced by looking at how much is saved with them vs. without or with current treatments, including patient deaths and hospitalization, which are expensive for the healthcare system, and then pricing the new products a little bit lower to assure their perception as being cost-effective, overall providing health care savings.

In the U.S., insurance providers continue to increasingly effectively take control of prescriptions away from physicians, pharmacists and patients, through restrictive formularies or otherwise forcing use of products for which they have secured preferential prices. Or insurers often simply just refuse to pay for expensive biopharmaceuticals that they (not the prescribing physician and patient) do not consider the most appropriate (cost-effective/cheapest). As biosimilars become available, much as with generic drugs, U.S. insurers will surely force physicians, pharmacists and patients to use these rather than more expensive innovator products. This is fully expected, much as most payers currently push patients to fill drug prescriptions with generics. Otherwise, biosimilars may not be included in payers' formularies, as insurers cut discount deals with the reference products' manufacturers and simply avoid use of biosimilars.

Outside of the U.S. government-imposed price controls are common, if not the general rule.

This includes the U.K. National Institute for Health and Clinical Excellence (NICE) issuing product reviews, including rejecting some biopharmaceuticals as too expensive and not cost-effective for use by the country's National Health Service (NHS), effectively making these products nonmarketable in the U.K. Many other countries in Europe and the rest of the world take an even more proactive and intrusive approach to negotiating or simply setting/limiting much, most or all pharmaceutical prices. In many respects, the U.S. clear lead as the source for innovative (bio)pharmaceuticals is largely due to it offering the most incentives to developers, providing the most rewards/profits for those successful at getting innovative products approved and marketed.

Manufacture in Developing Countries is Increasing: Biopharmaceutical manufacture outside of the usual major market countries is increasing, as indicated by BioPlan's free online Top *1000 Global Biopharmaceutical Facilities Index* (www.top1000bio.com), which ranks facilities worldwide in terms of known or estimated capacity, products manufactured and employment. This includes much expansion of manufacturing capacity, including new facilities, in China, India and other Asian countries. The situations in China and India are further discussed in a later section. This manufacturing is nearly all exclusively for domestic, regional and/or lesser- and non-regulated international commerce, with hardly any biopharmaceutical manufactured in developing countries marketed in developed countries.

Much of the world's biopharmaceutical commerce involves developing countries-based companies purchasing and distributing biogeneric products that receive little or no regulatory evaluation. Many developing countries healthcare systems issue tenders (RFPs) and purchase their country's biopharmaceuticals, generally biogenerics (see biosimilars section below), from the lowest bidder internationally. These sources essentially just serve as 1-off CMOs, with no real product testing or approvals, with manufacturing not meeting GMP, etc. Rarely, are such products ever in any way rigorously tested, such as analytical (beyond basic compendial confirmation of API identity) and clinical testing. Often there are no clinical trials at all with these products Contractors simply make the product to the specifications called for, with this often involving just meeting the very broad active agent product descriptions set by a selected pharmacopeia, e.g., USP.

Often, the biogeneric product's full development and manufacturing costs are less than the costs of doing basic biosimilarity analytical testing, cell banking, or any other tasks involved with gaining major market approvals and manufacturing to GMP standards. There are cases where all the manufacturer must do is provide a sterile product containing the needed amount of active agent as specified by its INN (generic name), with testing for purity, potency, GMP-quality manufacturing, etc., not a concern. Many countries lack sufficient funds to purchase GMP quality biosimilar/biogeneric products, much less innovative reference products, and simply have no alternatives than to seek out the absolute lowest-cost biopharmaceuticals. And in many cases, this may well be the right thing to do. A poor country may face a choice of either providing a cheap lower quality version of a product, such as Factor VIII for hemophilia A or epoetin alfa for kidney failure, for its patient populations, keeping them alive but with higher incidence of adverse effects vs. purchasing high quality, more expensive, GMP-meeting products and supplying these to a smaller percentage of patients, but overall resulting in higher deaths and morbidity. For example, a developing country may decide to provide cheaper, lower-quality epoetin alfa that has serious adverse events among 1/1,000 patients, while in developed countries incidence of serious adverse events at just 1/10,000 would likely be noticeable and result in product recalls, withdrawals and liability/damage lawsuits, perhaps even death of that company.

Much new and increased manufacturing capacity is being added internationally. This includes more facilities to satisfy growing biopharmaceutical markets in many developing countries rapidly growing, with more domestic/ regional companies increasingly serving these markets. The products are generally biogenerics or other outright copies of innovator products that are simply marketed as substitutable for the innovator product (without much, if any, real analytical or clinical biosimilarity testing, and without GMP-quality manufacturing). Developed country-based companies seeking to expand in international markets will increasingly have to deal with such local/regional competition. This may require increasingly partnering and licensing with domestic manufacturers and/or marketers. The extent to which domestic markets in developing countries will adopt absolute cheapest 1-off manufactured-type biogeneric products vs. higher quality and more expensive products manufactured more to highly-regulated country standards remains to be seen. India appears to have made its choice, preferring to be the world's leading source for finished generic drugs and biogenerics. Patients and payers (including foreign governments, and payers, where there is any health insurance) in developing countries will continue to go with the cheapest products.

Another factor that will result in increasing biopharmaceutical manufacturing in many lesser-developed countries is that these countries' governments are slowly increasingly seeking to assure domestic manufacture of the biopharmaceuticals being sold in their markets. In many or most cases, government agencies or a government proxy/front company(ies) purchase and distribute biopharmaceuticals. Already, some countries are starting to tell vaccine manufacturers

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- Advances in Biopharmaceutical Technology in China, 2nd Ed., 2018, Soc. Ind. Microbiol, Biotech
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- Advances in Biopharmaceutical Technology in India
- Top 60 Biopharmaceutical Organizations in India
- Quick Guide to Biotechnology in the Middle East
- Quick Guide to Biofuels

The 15th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production is the most recent study of biotherapeutic developers and contract manufacturing organizations' current and projected future capacity and production. The survey includes responses from **222 responsible individuals** at biopharmaceutical manufacturers and contract manufacturing organizations from 22 countries. The survey methodology includes input from an additional **130 direct suppliers** of raw materials, services, and equipment to this industry. In addition to current capacity issues, this study covers downstream processing problems, new technologies, expression systems, quality initiatives, human resources and training needs of biopharmaceutical manufacturers, growth rates of suppliers to this industry, and many other areas.

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