BioPlan associates, inc.

APRIL 2019

TRENDS AND ANALYSIS FOR THE BIO/PHARMA INDUSTRY — 16 YEARS

SIXTEENTH ANNUAL

Report and Survey of Biopharmaceutical Manufacturing Capacity and Production

A Study of Biotherapeutic Developers and Contract Manufacturing Organizations

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- Patrick Evrard, Senior Principal Engineer Single -Use Technologies, Technical Communication and Regulatory Strategy, Pall Biotech
- Paul Spencer, Owner, PharmaMercenary
- Stefan Schmidt, COO/Head of Operations, BioAtrium 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)
- BIO (Biotechnology Industry Organization, Washington, D.C.)
- BioMaryland (Baltimore, MD)
- Bio-Process Systems Alliances/SOCMA (BPSA) (Washington, D.C.)
- bioLIVE, adjacent to CPhI Worldwide (Madrid, Spain)
- BioMaryland (Rockville, MD)
- Bio-Process Systems Alliance (BPSA) (Arlington, VA)
- California Life Sciences Association (CLSA) (San Francisco, CA)
- D2L Pharma (Bangalore, India)
- North Carolina BioSciences Organization (Research Triangle Park, NC)
- North Carolina Biotechnology Center (Research Triangle Park, NC)
- Pharma & Biopharma Outsourcing Association (PBOA) (Ringwood, NJ)

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)
- BioPharm International (Iselin, NJ)
- BioProcess International (Westborough, MA)
- BioProcess Online (Eric, PA)
- Contract Pharma (Ramsey, NJ)
- Pharmaceutical Manufacturing (Schaumburg, IL)
- Pharmaceutical Technology (Iselin, NJ)
- Pharmaceutical Technology Europe (Iselin, NJ)

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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Patrick Evrard joined Pall Biotech in 2017, as Senior Director, SLS Single-Use Technologies, to manage the technical team providing expert technical support to Pall Biotech's customers. Before joining Pall, he led for more than 10 years a global technical team in charge of developing and implementing single-use technologies in GSK Vaccines' commercial manufacturing operations. Patrick and his team implemented at global level single-use technologies in critical sterile applications and re-engineered several vaccines processes, switching from classical grade A open processes to closed systems. Mr. Evrard has written and contributed to several articles and white papers on single-use technologies, was part of the Board of Directors of the Bio-Process Systems Alliance (BPSA). He has been participating since 2012 in several single-use technology industry work groups, from BPSA, BioPhorum Operations Group (BPOG), American Society of Mechanical Engineers (ASME BPE) and ASTM International.

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Dr. Stefan R. Schmidt currently serves as COO/Head of Operations at BioAtrium AG, a Lonza and Sanofi JV in Switzerland. Previously he held the position as CSO and other senior executive roles at Rentschler Biopharma with overall responsibilities for development, production and innovation. Before that, he was CSO at ERA Biotech in Barcelona, directing the company's R&D efforts. Prior to that, he worked at AstraZeneca in Sweden where he led the unit of Protein Sciences as Associate Director. He started his leadership career in Munich more than 20 years ago where he built up protein biochemistry teams for Connex and GPC-Biotech. During his academic education he earned a PhD in Biochemistry and an MBA in Marketing.

Paul Spencer, Owner, PharmaMercenary

Paul Spencer has a BS in Chemical Engineering, an MBA, and is a licensed PE in two states. Mr. Spencer started his career in the fermentation and purification of Monoclonal Antibody based diagnostic products. This included work conjugating MAbs to diagnostic markers. Later work has involved research to commercials manufacturing of innovative therapies, as well as high volume/high completive products. Mr. Spencer has 35 years of technical experience in a many of the therapeutic facilities. He provides a highly technical capability to those pharmaceutical units due to his 35 years of experience. He is a person that has been involved in significant improvements to the marketplace, often considered a thought leader in multiple unit operations and technological developments.

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Business Development globally at Rentschler Biopharma with a strong contribution to the tremendous growth phase from 2013-2017 were sales more than tripled. Prior to joining Rentschler Biopharma, Christoph Winterhalter served as Vice President Biosolutions at Wacker Chemical Corporation in Michigan US heading a 100 MIL USD business for Life Science. Before that he held several positions at Wacker Chemie AG in Germany, where he started in 1995 to develop the first fermentation route to cysteine by metabolic design in *E. coli.* Christoph Winterhalter holds a Ph.D. in Microbiology at the Technical University of Munich.

16th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production • April 2019

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METHODOLOGY

This report is the 16th 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 221 qualified and responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations in 24 countries; plus 120 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 including regarding respondents' current capacity, production, novel technology adoption, human resources, quality, and outsourcing issues. We also 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, including monographs in Chapter 2. These monographs cover the events and trends that will shape biopharmaceutical manufacturing over the next five years. We also have included this year a chapter on Continuous Bioprocessing. Over the past few years, advances in technologies, expression systems, 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 cited in our acknowledgments section. In addition, to support this coverage, we also include acknowledgment of our media partners, whose assistance enabled us to reach the many high quality of respondents required in this quantitative analysis.

Further information on methodology, breakouts on specific segments, and data from earlier surveys may be requested 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, nearly 90% 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 16th year edition. We solicit and receive survey responses from individuals at organizations around the world. This year includes input from individuals based in 24 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 221 biopharmaceutical manufacturers and contract manufacturing organizations responding to this year's survey, 27.2% were primarily involved in *"Process development for biopharmaceutical manufacturing",* up from 27.0% in 2018 and 25.6% in 2017; and 26.7% were involved in *"Large-scale cell culture production for therapeutics",* an increase from 23.4% in 2018 and 25.1% in 2017. There was a sharp decrease to 10.9% for this year for those involved in *"Scale-up (or clinical-scale) production for biopharmaceuticals PRIMARILY",* compared with 15.8% in 2018 and 14.1% in 2017. But overall, the general pattern of type of organization of those surveyed did not change.

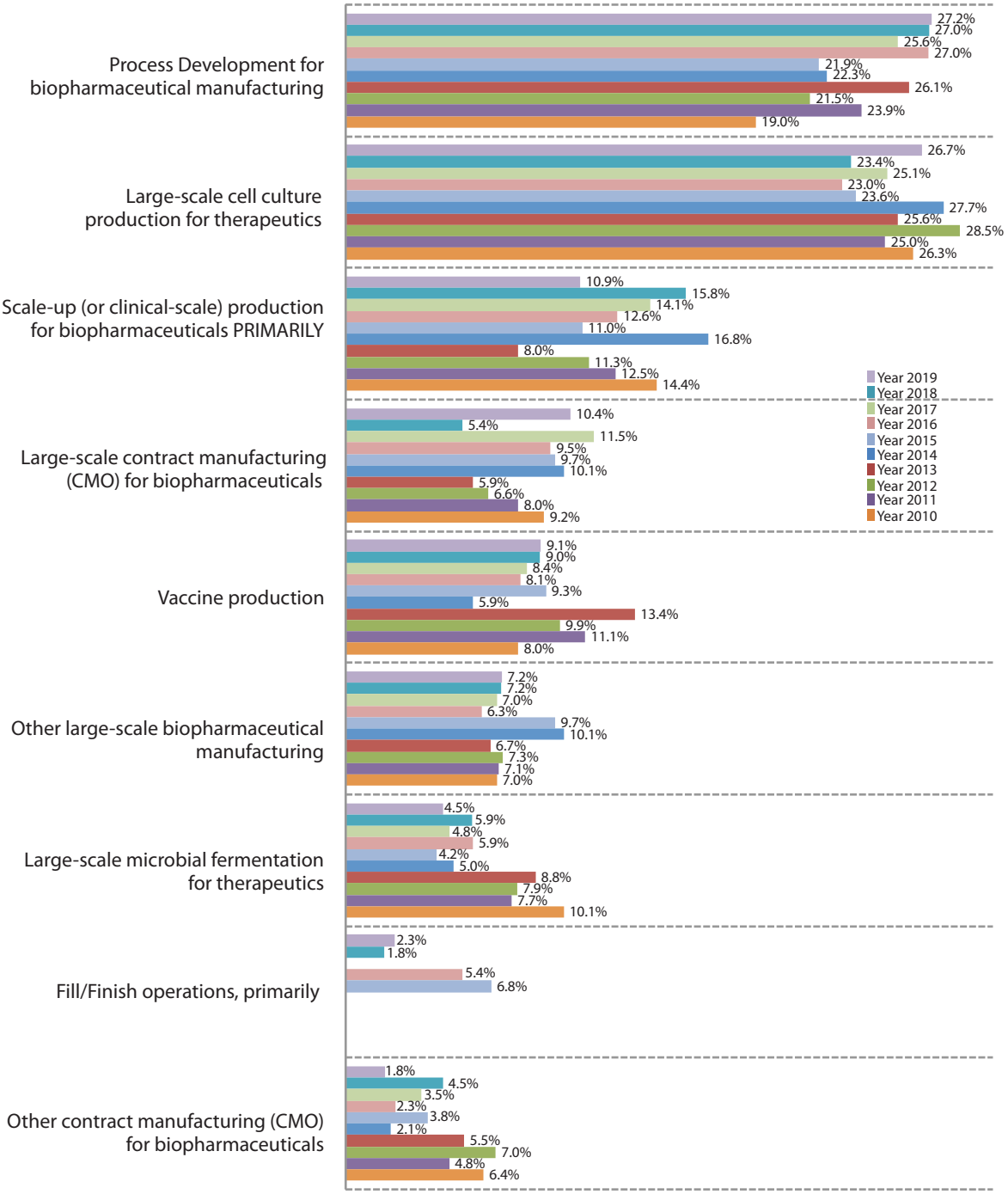
Respondents involved with *"Large-scale contract manufacturing (CMO) for biopharmaceuticals"* increased to 10.4% from 5.4% in 2018. *"Large-scale microbial fermentation for therapeutics"* dropped from 5.9% in 2018 to 4.5%, closer to the 4.8% reported in 2017. *"Vaccine production"* was 9.1%, virtually unchanged from 9.0% in 2018, which was a slight uptick from 8.4% in 2017. *"Other large-scale biopharmaceutical manufacturing"* accounted for 7.2%, the same percentage as in 2018, which was a slight increase from 7.0% in 2017. *"Other" contract manufacturing*

(CMO) for biopharmaceuticals" dropped sharply from 4.5% in 2018 to 1.8%, the lowest level reported since 2014 (2.1%). *"Fill/Finish operations"* accounted for 2.3%, a slight increase from 2018 (1.8%), but still much less than 5.4% in 2016.

Overall, the makeup of respondents remains consistent with prior years' surveys. Despite variations, including decreases, in involvement in aspects of biopharmaceutical manufacturing, this year's data continue to fall within the range generally defined by prior years' data reports, 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 2019

"In which area of biopharmaceutical manufacturing is your organization currently involved?" (2010 to 2019)

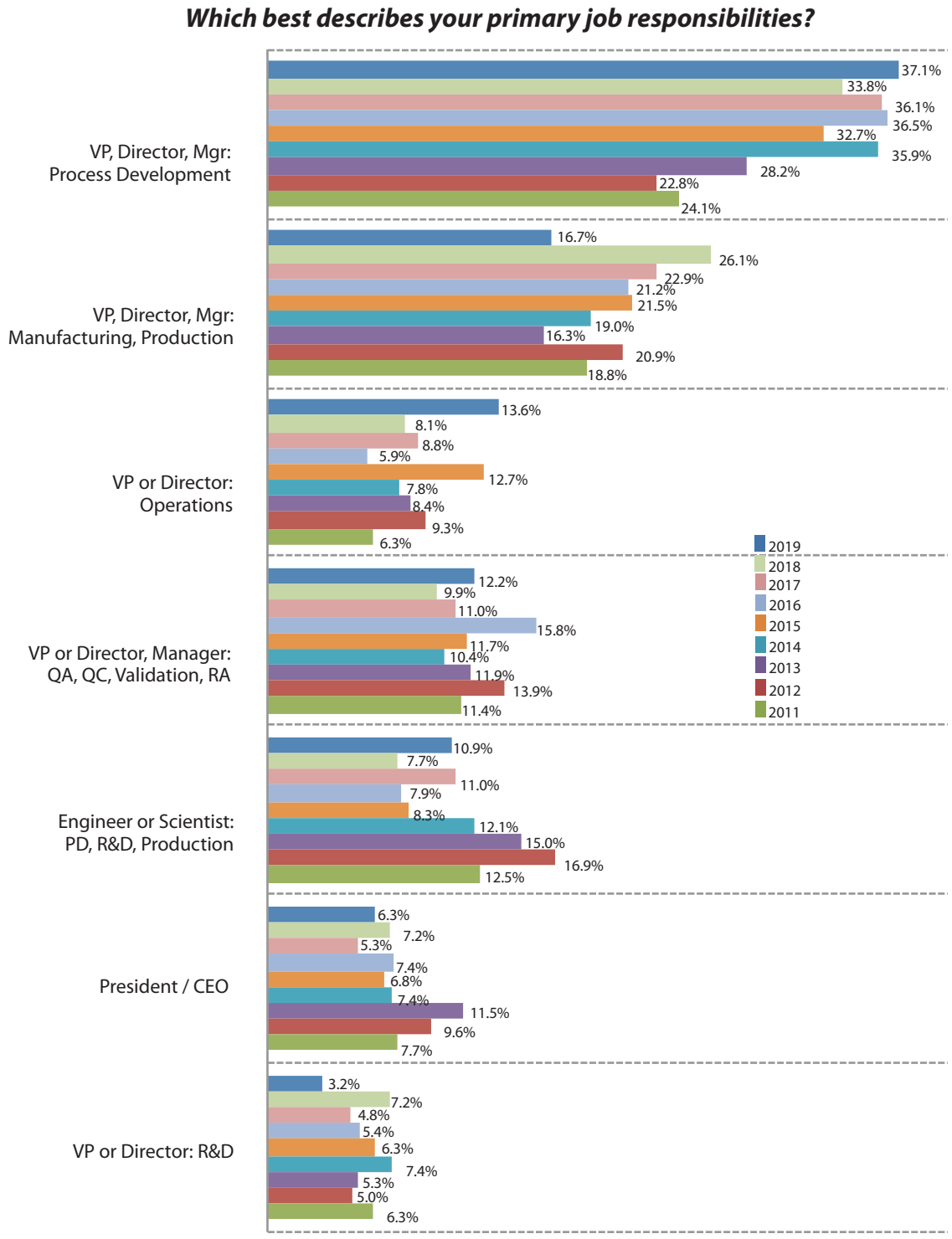


0-2 RESPONDENTS QUALIFICATIONS

Respondents were asked about their areas of responsibility, as indicated by job title (Fig. 0.2). Over 89% had a title of *"VP, Director, or President/CEO",* a slight decrease from last year's 92%, but still consistent with the levels since 2014, with an average of about 90% in recent years. This year, 12.2% of respondents were *"VPs, Directors or Managers of QA, QC, Validation, or RA",* an increase from 9.9% in 2018 and closer to the 11.0% in 2017, but not as high as 15.8% in 2016. The category "Engineer or Scientist: PD, R&D, and Production" (i.e., without VP/Director/Manager responsibilities) accounted for 10.9% of respondents, a marked increase from 7.7% in 2018, but overall a decrease from 11.0% in 2017.

"Presidents/CEOs" represented 6.3% of respondents, down from 7.2% in 2018 and 5.3% in 2017; and "VPs or Directors of R&D" accounted for 3.2% of respondents, a dramatic decrease from 7.2% in 2018 and less than previous years. The category *"VP or Director: Operations"* grew substantially to 13.6% in this year's survey, up from 8.1% in 2018 and 8.8% in 2017. *"VPs, Directors or Managers in Process Development"* again comprised the largest percentage of respondents at 37.1%, up from 33.8% in 2018 and 36.1% in 2017. Although *"VPs, Directors or Managers of Manufacturing and Production"* accounted for the next-highest percentage at 16.7%, this was much lower than 26.1% in 2018 and 22.9% in 2017. Combining *"VPs, Directors, and Managers in Process Development"* with those in Manufacturing and Production, the total is 53.8%, still representing most of the respondents, but less than the 59.9% in 2018. Overall, respondent job titles and levels of responsibility have changed little over the years.

Fig 0.2: Respondents' Job Responsibilities, 2011 – 2019

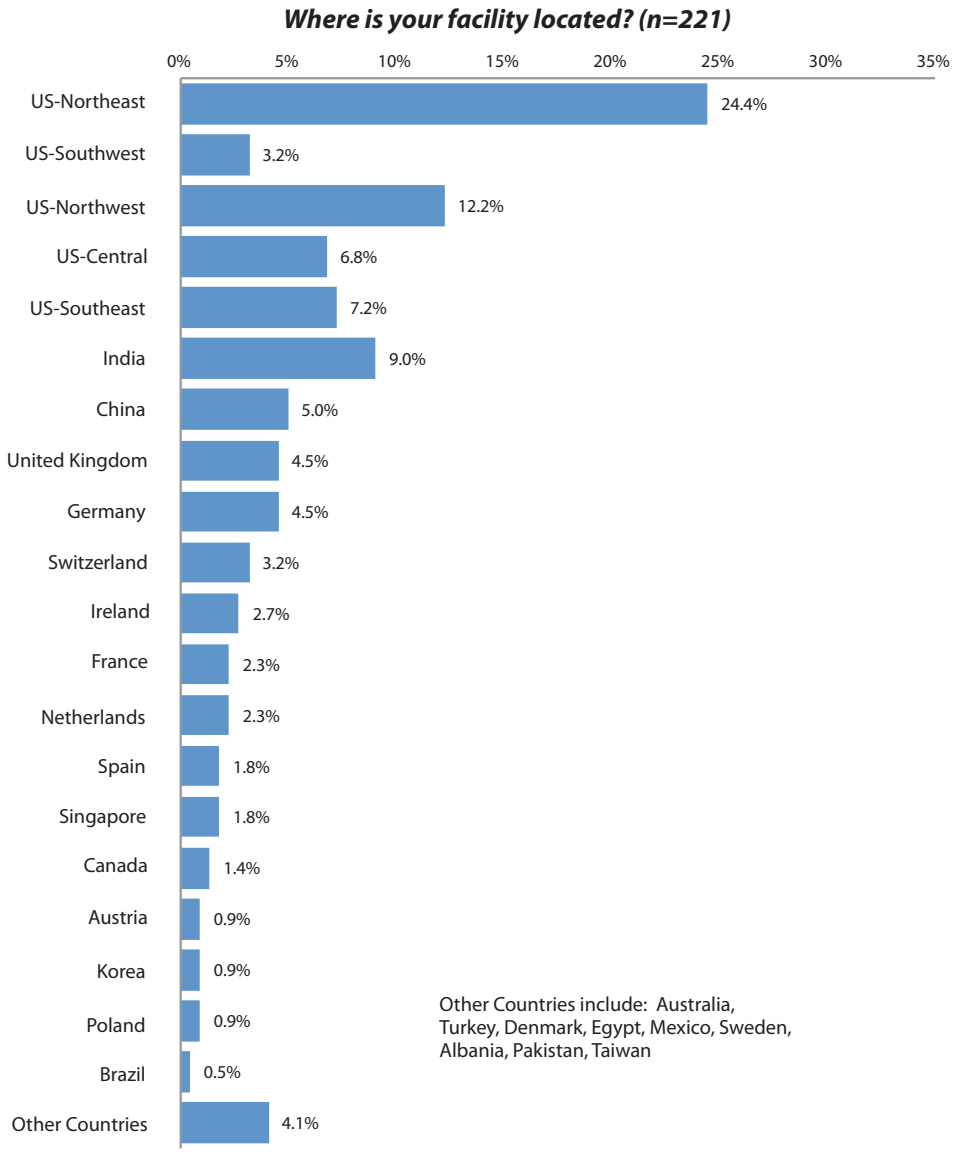


0-3 FACILITY LOCATIONS

This year, surveyed respondents were based in 24 countries (Fig. 0.3). Approximately 54% of the respondents were from the United States, with the Northeastern U.S. continuing to make up the largest group at 24.4%, a decrease from 27.9% in 2018 and 28.6% in 2017. Respondents from Western Europe made up just over 23% of the total, an increase from 18.9% in 2018 and closer to the 24% in 2017 and 21.4% in 2016. Asia is well represented, including a dramatic growth from 6.8% in 2018 to 9.0% in India, but a decrease from 8.1% in 2018 to 5.0% in this year's survey in China. Other countries (not covered by reporting of specific countries) continued to make up 4.1% of the respondents. The geographic distribution of respondents is similar to the distribution of bioprocessing facility capacity, discussed in sections below.

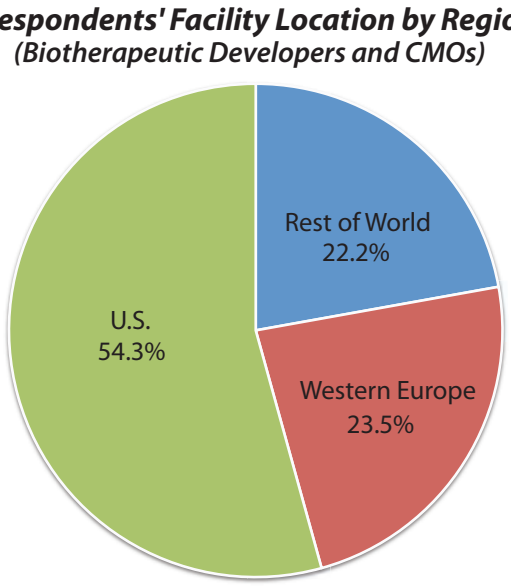
Further information about biopharmaceutical manufacturing facilities worldwide is available at the *Top 1000 Global Biopharmaceutical Facilities Index Web site* from BioPlan Associates (www.Top1000Bio.com)

Fig 0.3: Facility Location



We note that there was a slight decrease in U.S. respondents (54%) from 59% in 2018, 55% in 2017 and 61% in 2016 (Fig. 0.4). The percentage of Western European respondents (23.5%) increased somewhat from 18.9% in 2018, closer to the 24% in 2017 and the near constant 20% participation since 2011. This year ROW is represented by 22.2%, a slight increase over 21.6% in 2018 and 20.7% in 2017 and surpassing the peak 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, Thailand, 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 2019 (see Table 4.1) and changes over time (see Fig. 0.5). Percentages ranged from 74.2% *(Mammalian Cell Culture)* to 9.1% *(Plant Cells).* This year, we see a continued decrease in facilities using *"Mammalian Cell Culture",* down to 74.2% from 79.3% in 2018 and 81.1% in 2017. There was also a decrease in *"Microbial Fermentation"* systems to 43.5% from 47.8% in 2018, following a substantial increase from the previous year's 40.3%. Note: respondents were permitted to select multiple expression systems.

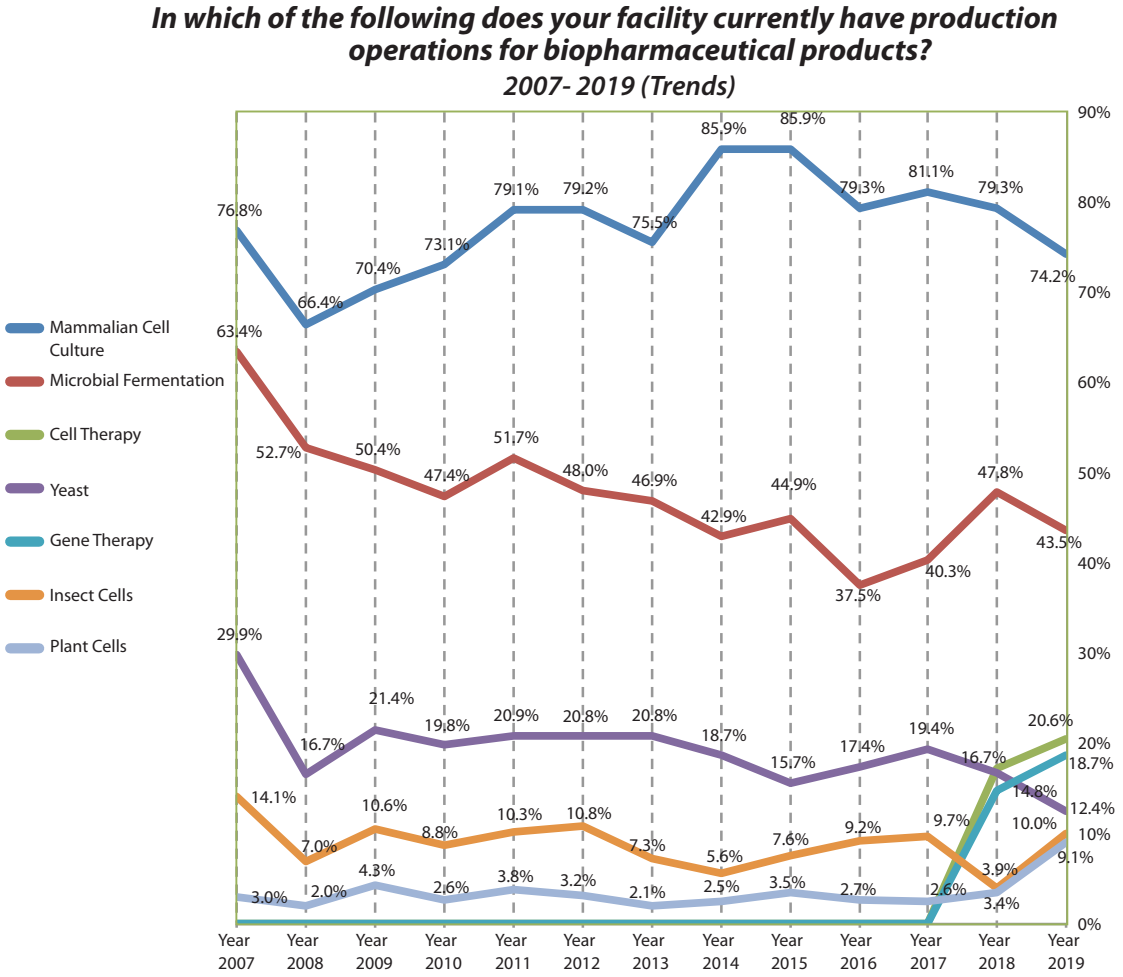
Also observed was a continued decrease in the overall percentage of respondents using *"Yeast",* from 19.4% in 2017 to 16.7% in 2018 to 12.4% this year. However, following a drop from 9.7% in 2017 to 3.9% in 2018, the use of *"Insect Cells"* rose substantially to 10.0%.

Following a steep increase from 2017 to 2018, *"Microbial Fermentation"* showed a decrease in 2019, from 47.8% to 43.5%. *"Cell Therapy* and *Gene Therapy",* on the other hand, continued to increase, to 20.6% and 18.7% in 2019, respectively. *"Plant Cells",* after a slight increase from 2017 to 2018 (2.6% to 3.4%, less than 1% above the 5-year average), jumped to 9.1% in 2019. The industry appears to be slowly increasing the diversity of basic expression systems/platforms in use.

Table 0.1 Areas of Biopharmaceutical Manufacturing Operations

Answer Options	Year 2019	Year 2018
Mammalian Cell Culture	74.2%	79.3%
Microbial Fermentation	43.5%	47.8%
Cell Therapy	20.6%	17.2%
Yeast	12.4%	16.7%
Gene Therapy	18.7%	14.8%
Insect Cells	10.0%	3.9%
Plant Cells	9.1%	3.4%

Fig 0.5: Biopharmaceutical Manufacturing Systems, (2007-2019) Trends



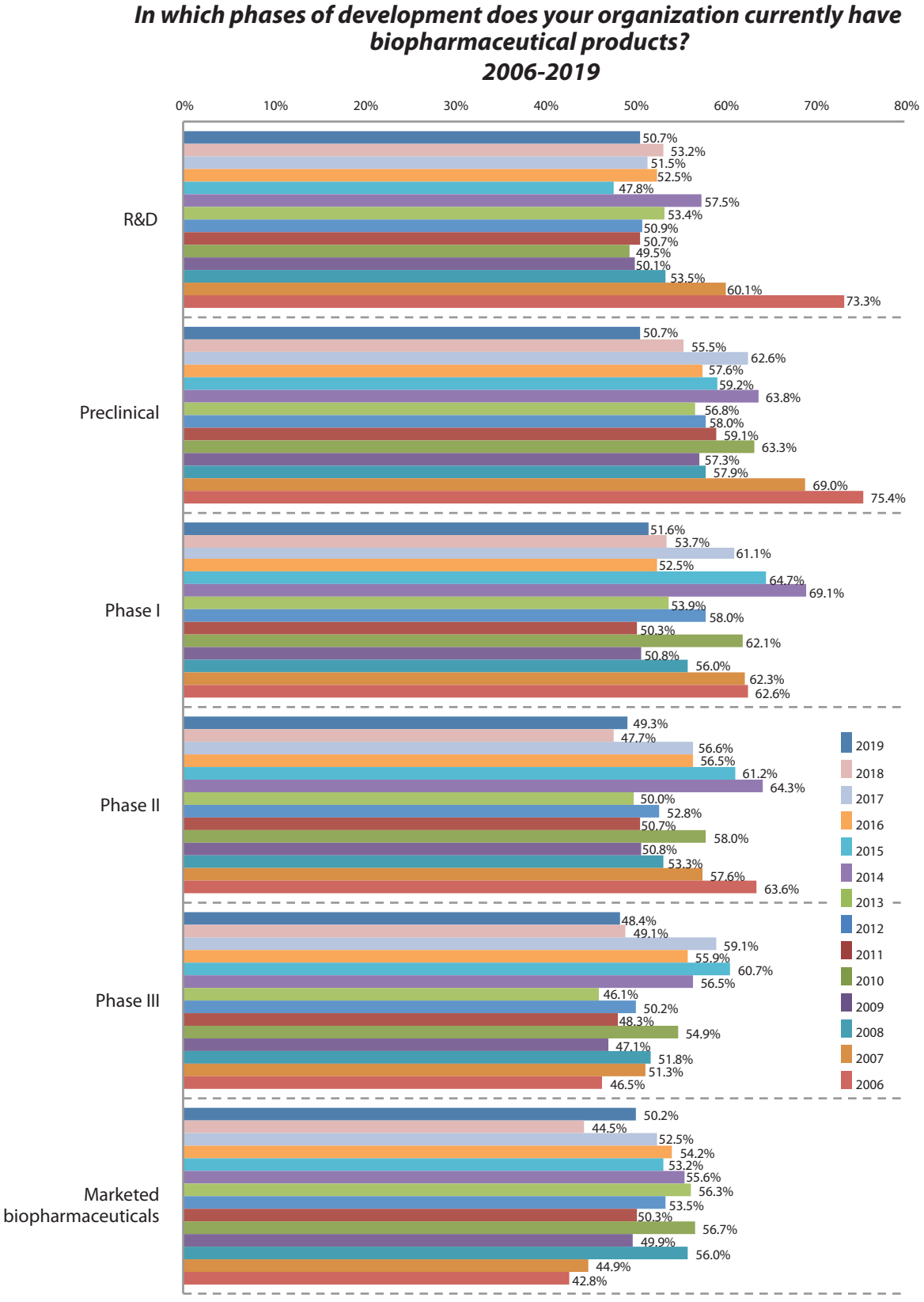
0-5 PRODUCTION OPERATIONS, PHASE OF DEVELOPMENT

We identified the phases of pipeline development in which respondents' organizations (companies) had products (Fig. 0.6). This year, slightly over half (50.7%) of companies had products at the *"R&D"* stage, a decrease from 53.2% in 2018. This reflects a continued shift in R&D back to the relative 50% level seen in almost all previous years, but is still much lower than the 73.3% reported in 2006. Facilities involved with *"Preclinical"* operations were at 50.7%, a decrease from 55.5% in 2018 and 62.6% in 2017. Note: respondents could indicate multiple phases of development for their facility.

This year respondents reported that 50.2% of facilities have biopharmaceutical products on the market, an increase from 44.5% in 2018 and closer to the 52.5% reported in 2017. Those working with *"Phase I"* development saw a drop from 61.1% in 2017 to 53.7% in 2018 to 51.6% in 2019. Facilities working with *"Phase III"* development had a slight drop from 49.1% in 2018 to 48.4% in 2019, following a 10% drop from 2017 that suggested a tightening of development pipelines. Hopefully, developers are making better choices regarding their product candidates, in terms of 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 approximately 50% of survey respondent organizations.

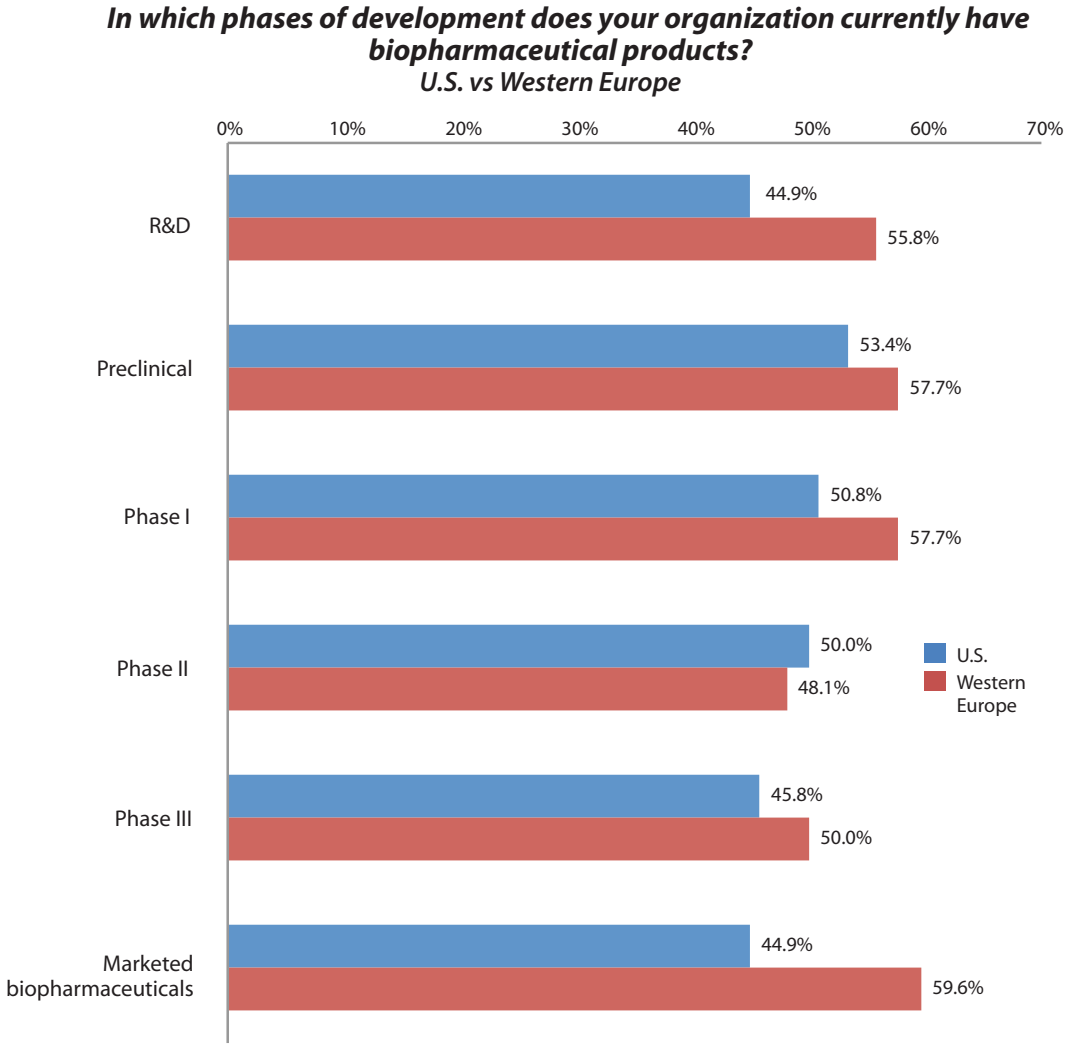
Fig 0.6: Phase of Development of Surveyed Respondents, 2006-2019



Western European respondents continued to indicate higher involvement by their companies with *"Preclinical"* products at 57.7%, while U.S. companies indicated lower involvement at 53.4% (compared to 58.5% vs. 54.7% in 2018), respectively. This is somewhat unexpected, in the context that overall the U.S. has more biopharmaceutical R&D facilities compared to Europe. This followed a reversal in 2017 from the previous year, when Western European companies showed lower involvement than U.S. companies (55.3% vs. 66.1%).

This year shows a greater difference between U.S. and Western European facilities in terms of *Phase I* clinical trials, at 50.8% vs. 57.7%%, respectively. . In 2018, the percentages were much closer at 53.1% vs. 53.7%, and in 2017, those reporting Phase I clinical trials in the U.S. far outnumbered those in Western Europe at 65.1% vs. 55.3%, respectively. Also seen this year is an increase in *Phase III* clinical trials in Western Europe at 50.0% (vs. 45.8% for the U.S.), compared to 2018 (39.0% vs. 51.6% for the U.S.), following a large decrease from 2017 (55.3% vs. 60.6% for the U.S.).

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



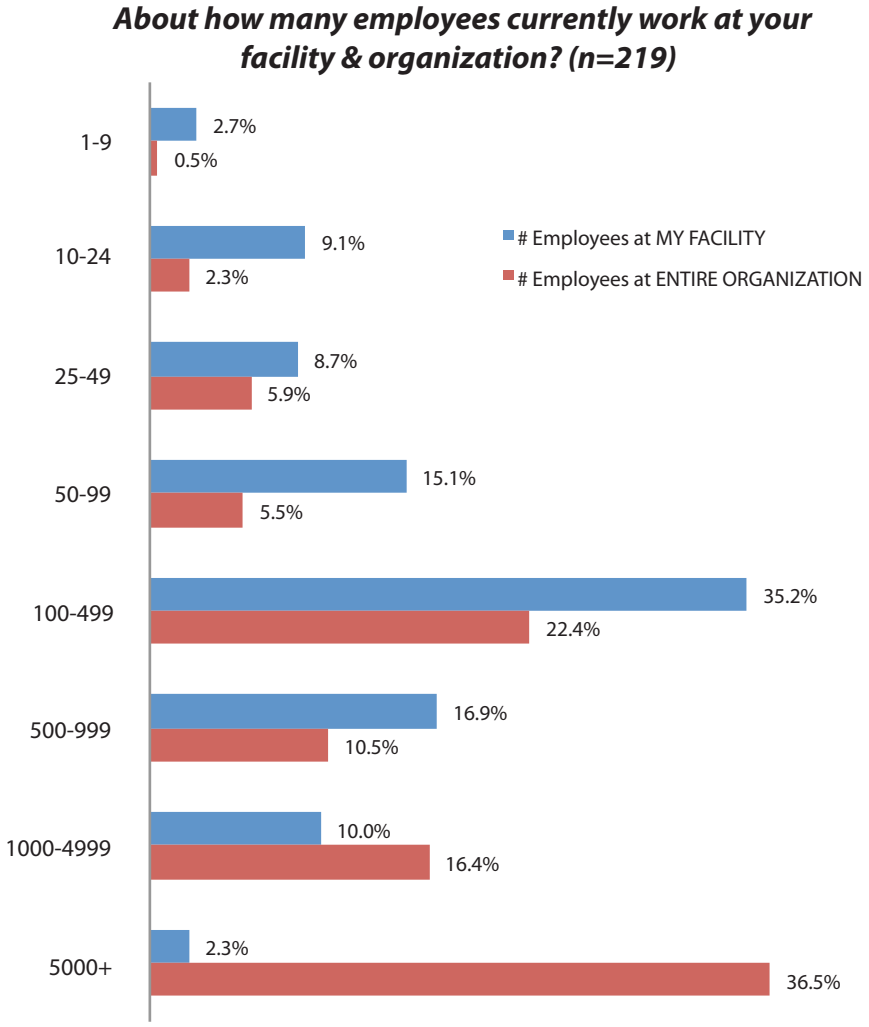
0-6 EMPLOYEES AT FACILITY

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 (Fig. 0.8).

The largest percentage of respondents continued to be at facilities with *100-499* staff members. Continuing a prior trend, the largest share of respondents, 36.5%, were from parent organizations with *greater than 5,000* employees, most of whom, as expected, were 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



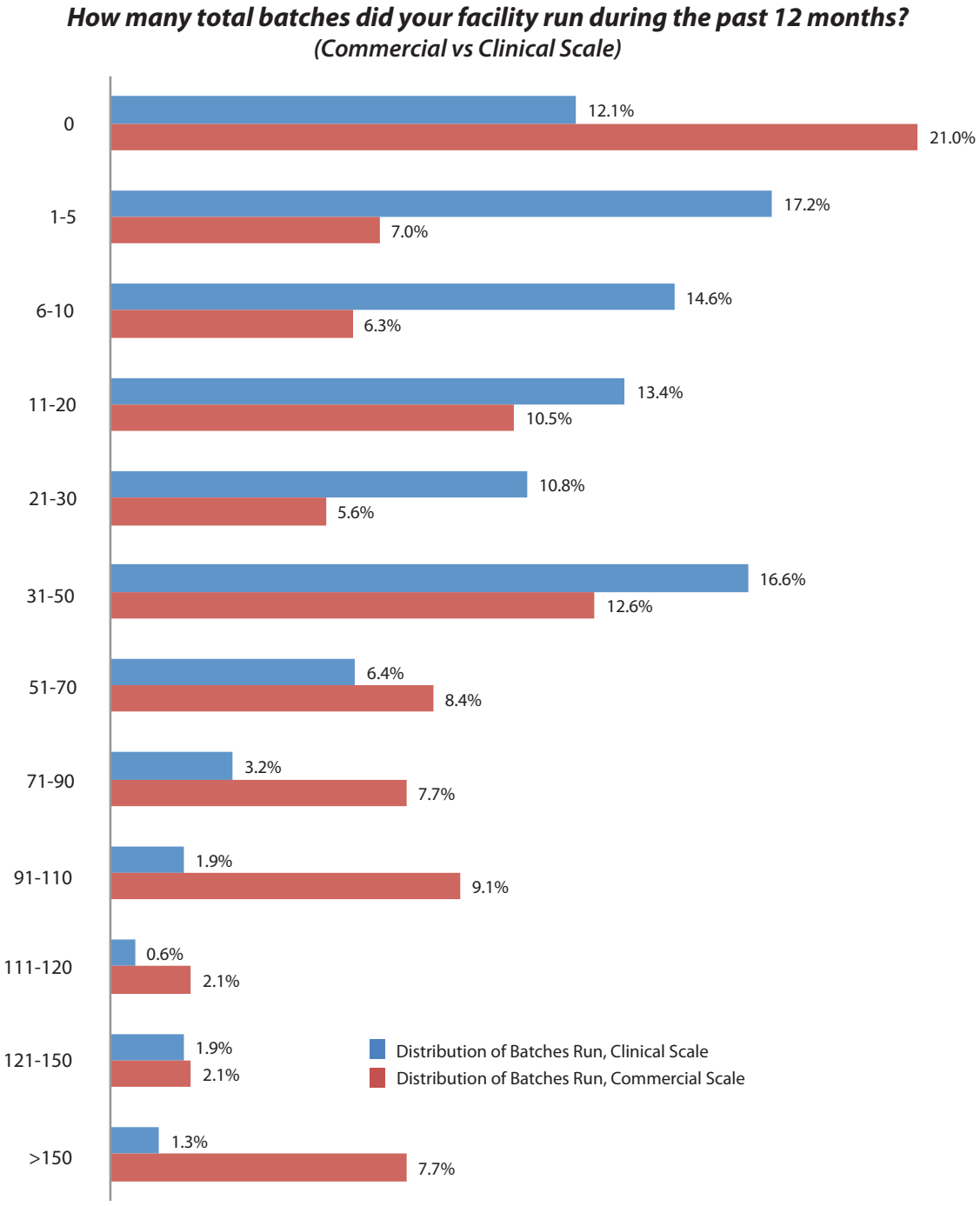
0-7 BATCHES RUN AT FACILITY PER YEAR

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 (Fig. 0.9).

We found that for *"Clinical Scale"* manufacturing, more than half of the facilities reported producing between 1 and 20 batches per year (57.3%), a more than 6% increase over 53.8% in 2018. At *"Commercial Scale",* only 7.7% reported producing over 150 batches per year, down from 8.7% in 2018 and 11.7% in 2017. The level of commercial scale manufacturing between 0-70 batches per year was 71.4%, down from 75.4% in 2018 and 75.9% in 2017.

This year, we saw decreases in runs of 0-10 batches compared to 2018 levels at both *"Clinical Scale"* and *"Commercial Scale",* from 50.4% to 43.9% and from 47.6% to 34.3%, respectively.

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



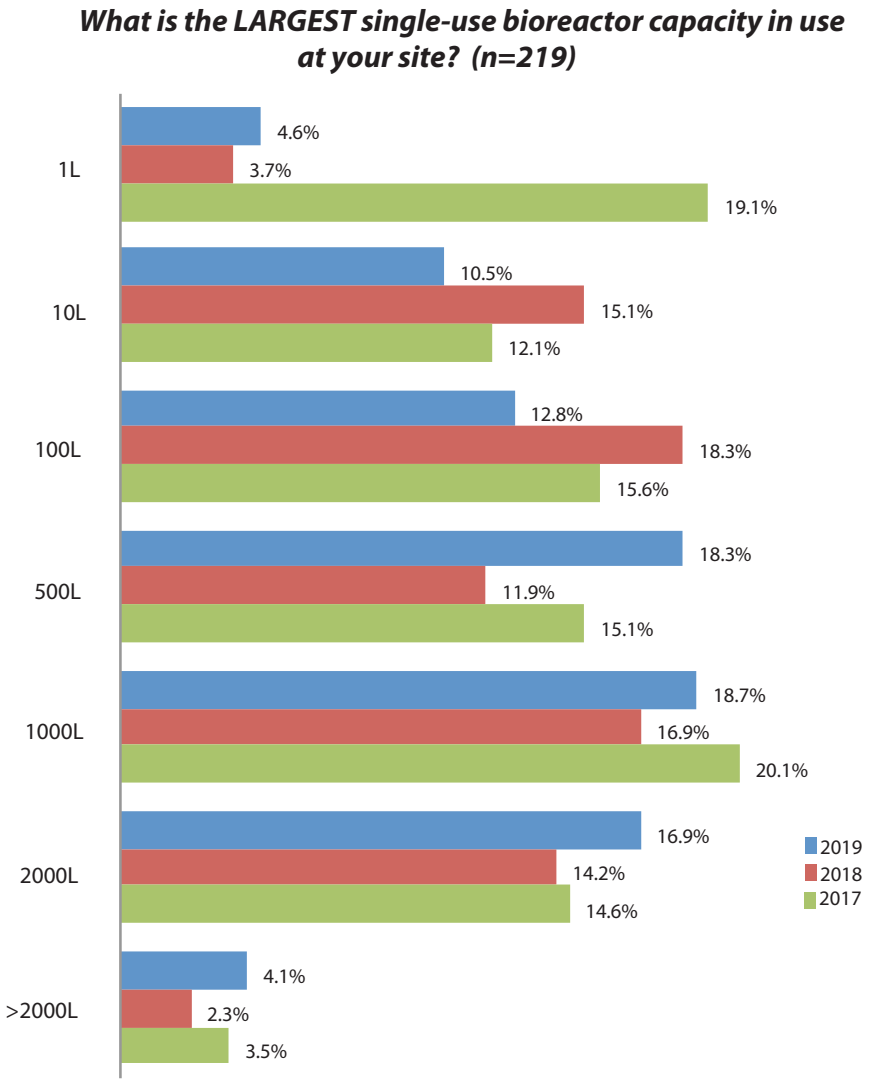
0-8 SINGLE-USE BIOREACTOR CAPACITY IN USE AT SITE

To follow the trend of single-use bioreactor capacity within the industry, we asked respondents again this year about the largest single-use bioreactor capacity in use at their site, in liters (Fig. 0.10).

The largest increase from 2018 was *500 L* capacity, jumping from 11.9% to 18.3% in this year's survey. The largest total percentage indicated *1,000 L,* at 18.7%, an increase from 16.9% in 2018 continuing to indicate likely late-stage clinical or even commercial manufacturing facilities. Behind *500 L* and *1,000 L,* the next highest percentage was again for *2,000 L,* at 16.9%, an increase from 14.2% in 2018.

More than one-third of respondents reported ≥*1,000 L* single-use bioreactors at their facilities, i.e., working at large scale by single-use standards, an 18% increase from 2018 (33.4% vs. 39.7%). As expected, few respondent facilities had single-use bioreactors with greater than *2,000 L* capacity, although, there was a significant increase over 2018, from 2.3% to 4.1%.

Fig 0.10: Distribution of Largest SINGLE-USE Bioreactor Capacity



0-9 STAINLESS STEEL BIOREACTOR CAPACITY IN USE AT SITE

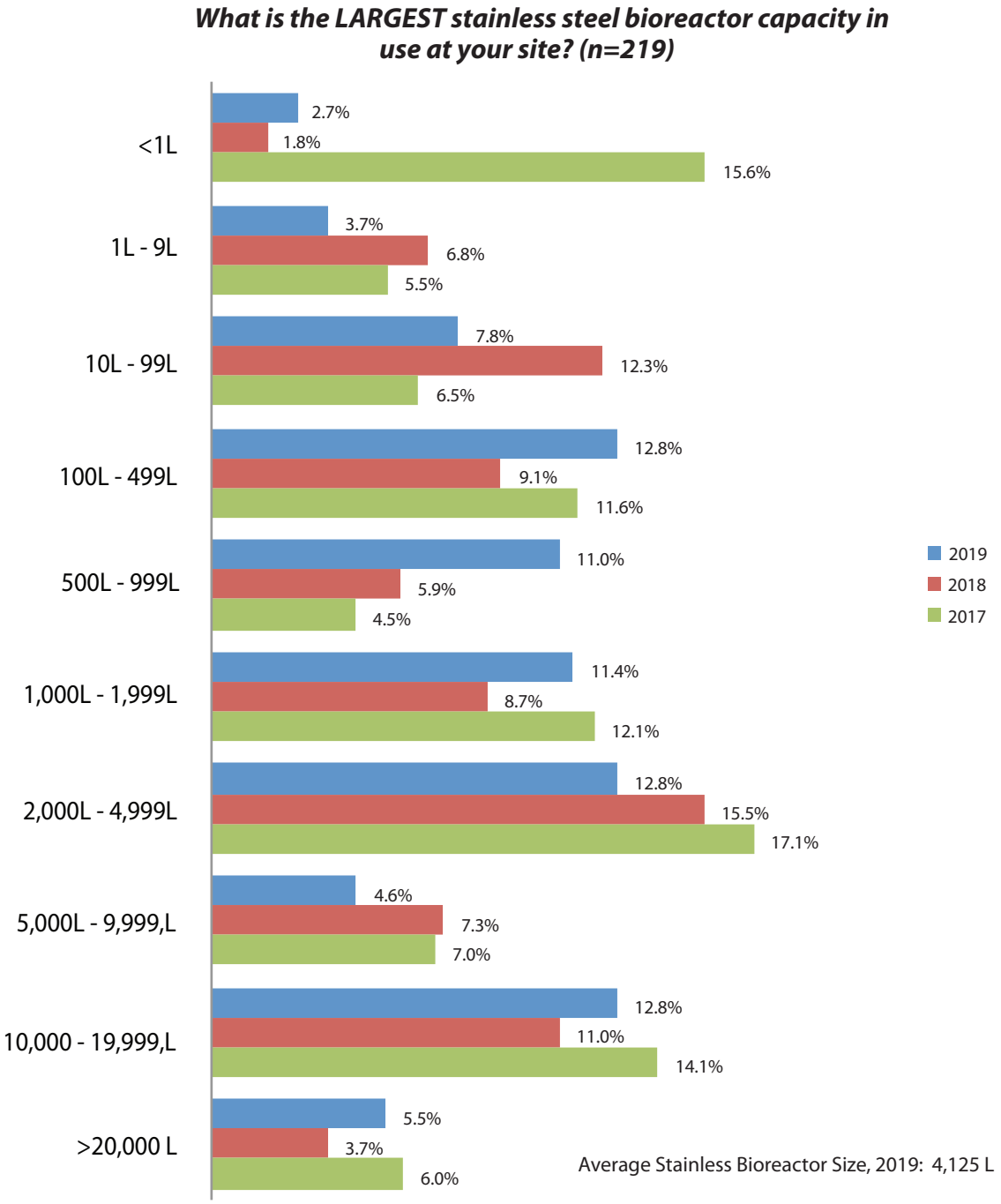
We continued to ask respondents again this year what was the capacity of the largest stainless-steel bioreactor at their facility (Fig. 0.11).

In 2019, the largest reported average size of on-site stainless steel bioreactors was 4,125 L, compared with an average of about 659 L for single-use bioreactors at survey respondents' sites.

The top three percentages reported were for 100–499 L, 2,000–4,999 L, and 10,000–19,999 L, each at 12.8%, compared to 2018, the largest percentages were for 2,000-4,999 L at 15.5%, followed by <10–99 L at 12.3%, and 10,000-19,999 L at 11.0%. The proportion with largest stainless steel bioreactors on-site with less than 1,000 L capacity increased from 35.9% in 2018 to 38.0%.

Comparing the data reported for the largest in-house single-use vs. stainless steel bioreactors, over one-third (35.7%) of facilities with stainless steel have ≥2,000 L bioreactors vs. 21.0% for single-use (compared to 37.5% and 16.5%, respectively, in 2018). This indicates increasing adoption of single-use bioreactors for entry-level single-use commercial manufacturing mostly involving use of 2,000 L single-use bioreactors.

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 its biopharmaceutical industry subset remain active, profitable and growing economic technology- and science-based activities and industries. This is despite about a decade ago having successfully survived the worldwide economic problems; the industry increasingly being targeted for criticism for excessively high prices; and biosimilars/biogenerics increasingly posing a threat to established products. There are estimated to be well over 10,000 therapeutics in R&D, both drugs (chemically-derived pharmaceuticals) and biopharmaceuticals (biotechnology- or living organism-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, now >1,700, products in the development pipeline, are follow-on biopharmaceuticals, mostly biosimilars and biobetters in major markets and a large number of biogenerics in lesser- and non-regulated developing countries and international commerce.

This 16th annual version of this publication continues to use consistent definitions for "biopharmaceutical" and "bioprocessing. "Biopharmaceutical" refers to pharmaceuticals, generally therapeutics, manufactured from and/or by living organisms; and the biotechnology processing involved is "bioprocessing." Source organisms are generally microbial, including nearly all sources for recombinant biopharmaceutical products, but can also come from other living organisms, e.g., Factor VIII or stem cells derived from pooled human blood/plasma. Biopharmaceuticals do not include pharmaceuticals that are synthetically manufactured or can be considered small molecule drugs. Generally, if a drug substance's (active agent's) structure can be represented or drawn without having to resort to use of names or symbols for component parts, such as amino acids with proteins and many fermentation products, including many antibiotics, it is a small molecule drug. Similarly, synthetic and purely semi-synthetic substances (e.g., purified enzymes used to drive chemical reactions) are not considered biopharmaceuticals.

The large number of biosimilars and biobetters in development indicate the maturation of the biopharmaceutical industry, as its current major blockbuster products and established platform technologies start to go off-patent. This represents a considerable shift in the biopharmaceuticals' product mix. Major changes brought be follow-on biopharmaceuticals include a rapidly increasing number of marketed biopharmaceutical products, particularly compared to as short as 5 or more years ago, and a number of new players entering the biopharmaceutical industry. The large proportion of industry R&D and manufacturing being devoted to follow-ons also contributes to basic shift in the pharmaceutical industry and

healthcare from small molecule drugs to biopharmaceuticals with increasing generic drug sector -like competition. This will accelerate in the U.S. market, the largest biopharmaceuticals' market, once FDA implements regulations for "interchangeable" biosimilars.

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 that this rarely happens, with much merger/acquisition activity apparently more to distract stockholders and boost appearances and through this stock value, while the new bigger post-merger/acquisition companies almost invariably soon consolidate and cut-back their combined R&D pipelines, close facilities, outsource more tasks previously considered better done in-house, etc. Luckily, this trend is slowing, although this could just be from there being fewer big-time players to allow much additional merging and purging among the largest companies. But in terms of biopharmaceuticals, any decreases in existing player company R&D is likely 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 moving into the biosimilar/biogenerics, cellular and gene therapies areas. As discussed below, the biopharmaceuticals industry keeps on expanding at a rather steady pace.

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 fewer promising candidates before they enter or earlier in clinical trials. This "failing faster," i.e., earlier in development, is generally much 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.

Along with more R&D and marketed products, 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 rather successful in their decade-plus efforts to co-opt the terms "biopharmaceuticals" and "biopharma," particularly in popular use, to apply to themselves and 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 terms "biopharma" or "biopharmaceutical" refer to biopharmaceuticals (biotechnology-manufactured) vs. just innovative or even all pharmaceuticals. PhRMA and many others now use the term "biopharmaceutical" with much consistency, but not to refer to actual biopharmaceuticals. The greater pharmaceutical industry and its hangers-on, including stock analysts and the trade press, often variably use the term with little consistency, and rarely ever explain the term's use/scope. Readers should use caution and inspect any definitions or scope notes provided where information about the "biopharmaceutical" or "biopharma" industry is being discussed. Many of those who use the term now are not using it with any explicit linkage to biotechnology (with biopharmaceuticals derived by biotech methods, i.e., manufactured using live organisms).

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 new entrants entering the field by developing biosimilars. These newer types of entrants, 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 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 with many new players entering the field, as our annual survey shows, most every current manufacturing facility is expanding its bioprocessing capacity in one way or another. 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 novel bioprocessing and biopharmaceuticals. The industry must continue to 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., with ever more diverse bioprocessing requirements.

The strategic importance of biopharmaceutical manufacturing and manufacturing capacity is increasing, and understanding the markets for biopharmaceuticals and bioprocessing technologies, industry capacity 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 periodically or even constantly. This can include cutting back on the number of products in their development pipelines or outsourcing of support and even critical tasks.

Effective planning within the (bio)pharmaceutical and bioprocessing markets is required to avoid problems later. This ideally involves a high level of leadership, partnership, information sharing, and communication between manufacturers, CMOs and bioprocessing technology and equipment suppliers as they develop and adopt 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 aware of the internal industry and external trends and issues affecting biopharmaceutical decision-making.

Many companies, even more affluent and 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 other companies are increasingly confident and are pushing ahead investing in in-house resources and doing full development and commercial manufacturing in-house. Prior rather common periodic 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. Many, particularly the largest biopharmaceutical companies.

Among many of the very largest companies, including Big Pharma, we still see cycles of short-term on-paper/theoretical profits and claims of synergies 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 and innovation, 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 cutbacks. While involved companies typically claim synergies, that their resulting pipelines will be better, that there will be more innovation, etc., this rarely happens as projected, but the new larger company lives on, with investors happy for the moment. But as the consequences of mergers and acquisitions and related consolidations and shedding of corporate resources and staff 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 such consolidations 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 therapies for diseases often ignored or currently untreatable, making them particularly welcome and needed. In recent years, this includes many products for orphan indications, with FDA and other regulatory agencies proactively supporting this. This includes FDA 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 innovative orphan therapeutics development, non-innovative biogenerics directed to lesser- and non-regulated international markets is where the growth is in developing countries. These markets are also but much less involved with development of biosimilars (with biosimilar approvals requiring extensive comparative clinical and analytical testing often not performed with biogenerics; generally restricted to more regulated markets). 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 biopharmaceutical industry. This is resulting in a significant increase in the number of biopharmaceutical players and manufacturing facilities, and as noted below, an increase in single-use-based manufacturing facilities.

Most large commercial biopharmaceutical manufacturing capacity expansions continue to involve building fixed stainless steel bioreactor-based bioprocessing systems, with commercial manufacturing using single-use systems just getting started. In the extreme, large stainless steel facilities coming online are exemplified by Samsung and Celltrion in S. Korea. Celltrion has reported plans to expand from its already super-size 140,000 L to 330,000 L capacity. This continued use of stainless steel at the largest scales is in contrast with production of supplies for R&D and clinical testing, which is now dominated by use of single-use/ disposable bioreactor-based systems, with this requiring much smaller bioreactors, facilities and infrastructure investment. About the only area of pre-commercial manufacturing not substantively using single-use systems at least is microbial fermentation, which generally continues to remain unchanged. Microbial fermentation continues to use much more extreme conditions (mixing, higher temperatures, etc.) than mammalian cell culture, with this restricting use of single-use systems. Overall, we are early in what will likely be a significant trend of developers adopting single-use systems for commercial product manufacturing, often involved scaling-out with multiple ≤2,000 L 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. A good portion 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

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The 16th 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 **221 responsible individuals** at biopharmaceutical manufacturers and contract manufacturing organizations from **24 countries**. The survey methodology includes input from an additional **120 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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