BioPlan associates, inc.

2019

Top 15 Trends in Biopharmaceutical Manufacturing, 2019

A Summary of Current Major Trends Affecting Biopharmaceutical Manufacturing from the

16th Annual Report and Summary of Biopharmaceutical Manufacturing Capacity and Production

Oct. 2019

Abstract: This review of the Top 15 Trends in Biopharmaceutical Manufacturing (bioprocessing) provides top-level trends information primarily from the 16th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, April 2019, published by BioPlan Associates.1 This is the most extensive and longest-running annual survey of bioprocessing professionals. We have drawn these insights and the ranking of trends based on an internal analysis of the trends observed, and with input from BioPlan's Biotechnology Industry Council™, an advisory panel of over 700 global biopharma industry subject matter experts. For information, visit www.bioplanassociates.com/16th

INTRODUCTION

This brief analysis summarizes just a few of the nearly 500 pages of data and findings over the past 16 years. The full study is available at (www.bioplanassociates.com/16th).

The biopharmaceutical industry continues to grow in size and diversity, including many new areas moving into the mainstream, e.g., cellular and gene therapies and live microbes as therapeutics. BioPlan's 2019 16th *Annual Report and Survey of Biopharmaceutical Manufacturing* (the "*Annual Survey*") shows that the industry and related opportunities continue to expand. As part of our annual analyses of biomanufacturing (bioprocessing), this year we surveyed 221 decision-makers at developer and contract manufacturing organizations (CMOs) in 24 countries. To assess industry growth and challenges from suppliers' perspectives, we also surveyed 120 industry supplier/vendor respondents.

The *Annual Survey* quantitatively evaluates the current industry situation and trends, and where it is going. This summary provides selected insights into broad trends, including:

- Industry size, growth, number of products, etc.
- Demand for efficiency
- International biomanufacturing
- Cell and gene therapy
- Hiring and training of staff

Overall, the pharmaceutical industry and its and biopharmaceutical subset remain active, growing and profitable. This very top-level finding has now been reported for 16 years, with the industry (revenue and nearly every other parameter) continuing to grow rather consistently at ≥12% annually, nearly doubling every ≥5 years. There are estimated to be well over 10,000 therapeutics in R&D, both drugs (chemical substances) and biopharmaceuticals (biotechnology-derived pharmaceuticals), with nearly 40,000 ongoing clinical trials. Among these, >40% or well over 4,000 candidate pharmaceuticals in R&D are biopharmaceuticals (manufactured using biotechnology/living organisms). A significant portion, now >1,600 products, in the development pipeline are follow-on biopharmaceuticals, mostly biosimilars (>1,000) and biobetters (>550) (see the *Biosimilars/Biobetters Pipeline Directory*, http://www.biosimilarspipeline.com, marketed by BioPlan). With continued steady growth in revenue, the worldwide biopharmaceutical industry is continuing to grow and expand, including in terms of facilities, capacity and staff, with the most rapid growth in developing countries (starting from low baselines).

TRENDS IN BIOPHARMACEUTICAL MANUFACTURING AND THE INDUSTRY

The biopharmaceutical industry is continuously growing, evolving, diversifying and demanding new and improved bioprocessing technologies to reduce costs, increase efficiencies, comply with safety and regulatory requirements, and improve weak development pipelines. Many of the largest pharmaceutical companies today are devoting increasing development efforts to biopharmaceuticals rather than small molecule drugs.

Multiple sources continue to report that most of the current major pharmaceutical companies, including Big Pharma, are spending 40%-50% of their R&D on biopharmaceuticals development, with this percentage slowly increasing. And there continues to be a very strong component of smaller, mostly innovation-oriented biopharmaceutical developer companies, increasingly in developing and not just major market countries. Incremental innovations in improved manufacturing productivity continue, exemplified by multiple decades rather steady increases in average upstream titers. Innovations also speed discovery, increase manufacturing options, and can drive down costs and improve overall productivity. The current situation in the biopharmaceutical industry is exciting, with new technologies and markets, such as biosimilars, cellular and gene therapies, and many new opportunities in emerging markets.

We project an optimistic future vision that includes the likelihood of more:

- Biological products, but often each with smaller markets, including more orphan and even personalized products
- Biopharma facilities worldwide, especially in major markets and Asia
- Cellular and gene therapies facilities and products, including commercial manufacturing
- Use of single-use systems, including fewer new commercial scale stainless steel-based facilities
- Modular-constructed facilities and cleanrooms
- Cloning or otherwise construction of major market GMP facilities in developing countries
- Follow-on products and manufacturers, including biosimilars, biobetters and biogenerics, with these capturing growing market shares
- Flexible manufacturing facilities, including use for manufacture of multiple

products
- Adoption of single-use systems at clinical scales and for commercial production
- Efficiency in bioprocessing as titers and yields continue to incrementally increase
- Adoption of continuous processing, including upstream perfusion and continuous chromatography for downstream processing
- Diverse and novel products in development and marketed, e.g., cellular and gene therapies; novel antibody frameworks; antibody-drug conjugates (ADCs); live microbe therapeutics, etc.
- Process automation, monitoring, control and data recording/processing built into bioprocessing equipment
- Use of bioprocess modeling, data mining, PAT, QbD, etc., with down-scale modeling in desktop, mini- or even micro-bioreactors increasingly important
- Use of improved expression systems and other genetic engineering advances
- Complex regulations which drive many other specific needs and advances

The 15 of the 'top' or major trends driving these and other changes in the biopharmaceutical industry are discussed below. Note: These are not presented in a particular order.

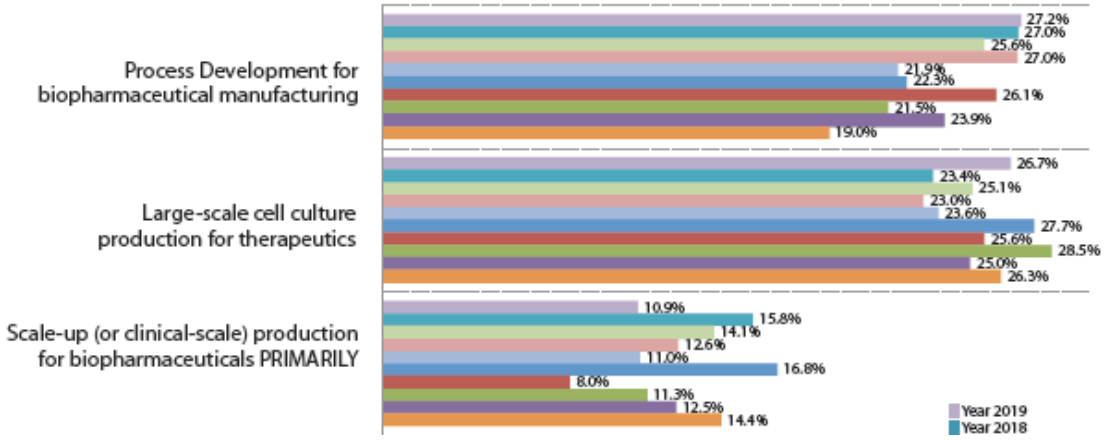
TRENDS Analysis

#1 Trend: More companies/facilities performing process development in-house

In the recent annual survey, 27.2% of respondents noted that their organization is currently involved with process development. There has been an overall increase since 19.0%, reported in 2010. Other data indicate that these facilities are primarily involved in commercial processing and process development. This includes 26.7% of respondents now reporting performing “Large scale cell culture production for therapeutics,” with no clear trend for this parameter; and 10.9% reporting “Scale-up (or clinical-scale) production for biopharmaceuticals PRIMARILY.”

Although not specifically surveyed, much of the increase in in-house process development is likely replacing use of CMOs for process development. A perhaps related trend contributing to companies/facilities seeing a need to have process development capabilities in-house is the increased scarcity of experienced bioprocessing professionals.

Fig 1: Area of Primary Involvement in Biopharmaceutical Manufacturing, 2010 to 2019



Source: 16th Annual Report and Survey Biopharmaceutical Manufacturing Capacity and Production, April 2019, BioPlan Associates, Inc. Rockville MD, www.bioplanassociates.com/16th

#2 Trend: Mammalian Systems Continue to Dominate Bioprocessing

Mammalian cell culture continues to dominate biopharmaceutical development and manufacturing, with this reflected in survey data, e.g., use of mammalian cell culture is now reported as used by nearly 80% of respondents. Mammalian expression systems (cell lines, vectors and associated genetic engineering) continue to be preferred over other options, e.g., microbial systems, particularly for recombinant proteins and monoclonal antibody (mAbs) production. This even increasingly includes facilities adopting mammalian cell culture as their preferred in-house platform, often for all or as much R&D and early phase manufacturing as possible. This includes mammalian manufacture of products for which commercial manufacturing will involve switching to microbial or another non-mammalian bioprocessing.

mAbs remain the single dominant class of biopharmaceuticals in development and marketed, with all but a small minority of mAbs with truncated and other modified backbones expressed using mammalian systems. Chinese hamster ovary (CHO) cell lines continue to thoroughly dominate mammalian production, but other mammalian cell lines are tending to increasingly be used, e.g., HEK293.

Table 1 presents this year's top-ranking data (those types of bioprocessing reported by >20% of respondents) for the expression systems/basic approaches reported as used at facilities (with reporting of multiple types for each facility allowed). About 75% of facilities are substantially involved in onsite mammalian bioprocessing, vs. about 43% are doing microbial bioprocessing; and >20% are now doing cellular therapies bioprocessing.

Table 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%

However, at the smallest scales, such as desktop and smaller scales used for high throughput screening and other initial candidate product expression, E. coli bacteria with inclusion bodies continue to dominate, with nearly all developers preferring to switch to

mammalian systems for clinical and GMP manufacturing, presuming cost-beneficial manufacturing can be done using mammalian systems. Many products, such as those requiring glycosylation, continue to essentially require mammalian manufacture.

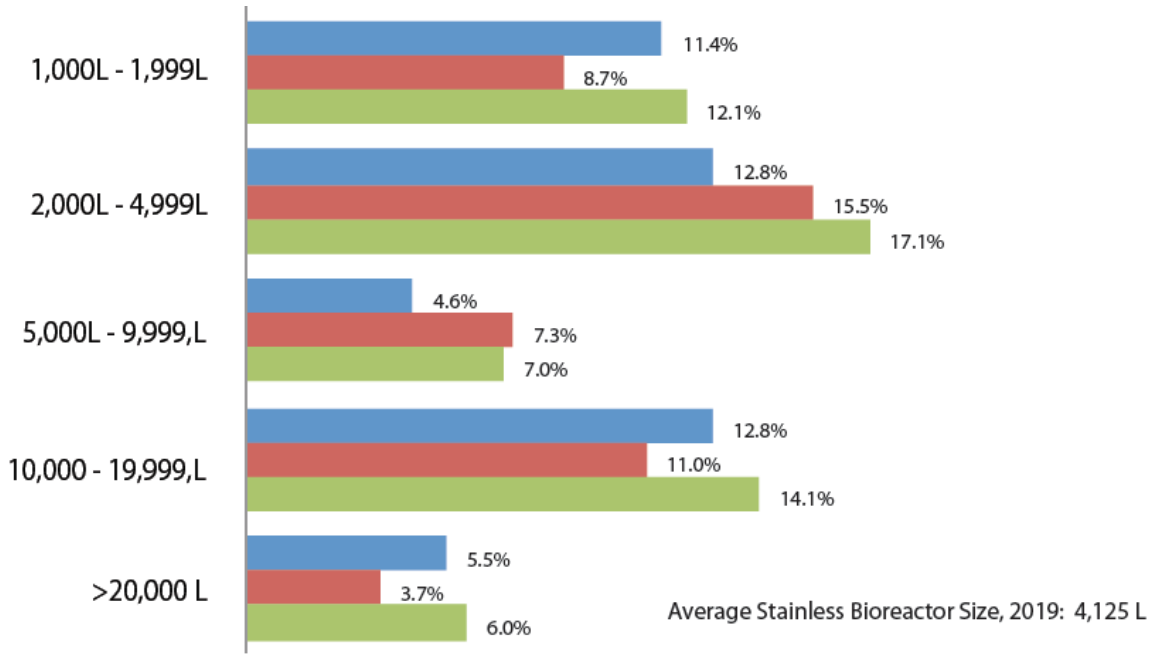
There are continuing incremental increases in mammalian system titers and yields (see related trend discussion). And with mammalian cell culture so predominant, mammalian culture is increasingly all that many bioprocessing professionals are now knowledgeable about, particularly for GMP or at any larger scales. For this and other reasons, many facilities continue to standardize their bioprocessing platforms using mammalian vs. microbial systems. In some cases, this even includes products that could be manufactured in microbial systems, which are generally still cheaper or more productive, but are now often initially being manufactured in mammalian systems, if these get the job done well enough, such as to produce pre-clinical or early clinical supplies. Trends and technological advances continue to favor mammalian over microbial bioprocessing, including trends for increasing titers and increasing higher proportions of products entering the development pipeline being mammalian expressed.

#3 Trend: Stainless Steel Bioreactors Are Becoming Smaller

Survey responses this year confirm a trend for reduction in the largest sized stainless steel bioreactors at facilities. There has been an overall decrease in the percent of respondents reporting their facilities having bioreactors ≥2,000 L, with 2,000 L generally the current cut-off for use of single-use bioreactors, with essentially all bioreactors >2,000 L being stainless steel. One company, ABEC, is marketing larger, e.g., 4,000 L, single-use bioreactors, but reportedly only about a dozen facilities are using these worldwide.

As shown in Fig 2 below, when asked to cite the capacity of the largest stainless steel bioreactor onsite, the average size was 4,125 L. For comparison, the average reported size of the largest single-use bioreactor onsite was 659 L. The number and proportion of facilities with their largest stainless steel bioreactor being <1,000 L has been increasing and is now 38%.

Fig 2: Largest Stainless Steel Bioreactor Capacity in Use at Facility Site, 2019



Source: 16th Annual Report and Survey Biopharmaceutical Manufacturing Capacity and Production, April 2019, BioPlan Associates, Inc. Rockville MD, www.bioplanassociates.com/16th

As new stainless steel bioreactors tend to be smaller, trends for largest onsite stainless steel bioreactor with <2,000 L capacity are starting to show increased use of stainless steel bioreactors in the 100-2,000 L range. This is despite these bioreactors being in the single-use range. The reported percentages of stainless steel bioreactors in this range all increased this year. This apparently involves new(er) stainless steel bioreactors coming online being smaller and more productive, such as operating at higher titers or using perfusion. Smaller stainless steel bioreactors are also likely increasingly replacing larger stainless steel ones, besides new stainless steel facilities and process lines going with smaller bioreactors. Overall, hardly any new facilities now under construction are anchored by stainless steel bioreactors. Exceptions include new super-sized facilities, such as Samsung in S. Korea.

Stainless steel bioreactors remain favored for many applications, particularly commercial manufacturing where it remains more cost-effective to invest in product manufacturing-dedicated facilities anchored by recyclable stainless steel bioreactors and all the associated infrastructure, e.g., in-house water for injection (WFI) production plant. Stainless steel equipment can handle much larger capacities compared to single-use, generally are more cost-effective at large scales, and remain the preferred method for large scale commercial manufacturing. Despite all the associated needed infrastructure and capital investment costs, stainless steel bioprocessing remains more cost-effective compared to single-use for long-term repeated or non-stop commercial manufacturing. In sharp contrast, as discussed below, single-use bioreactors now extensively dominate use for R&D and Phase I and II clinical manufacturing, with an estimated ≥85% of pre- and clinical bioprocessing using single-us systems.

#4 Trend: Healthy Biopharma Industry and Supplier Sector Growth

The biopharmaceutical industry and its associated suppliers, both equipment and services, have been growing rather consistently at ≥12% in terms of revenue over the past 20+ years. Worldwide sales of biopharmaceutical are now approaching $300 billion. With a very healthy pipeline of innovative and follow-on products and growth in international sales, industry revenue can be expected to further steadily increase and drive further growth in biopharmaceutical R&D and manufacturing. As noted in another section, the number of biopharmaceuticals in development is now approaching 5,000, with mainstream large international pharmaceutical companies, those with by far the largest R&D and marketing capabilities, now having biopharmaceuticals as >40% of their development pipeline. Biopharmaceutical developers, particularly those seeing success in clinical trials, suppliers, CMOs and CROs continue the pattern of often being acquired by a much larger company, another indicator of a healthy biopharmaceutical industry. New and innovative product types in development continue the trend of increasing the diversity of biopharmaceutical types in development, such as cellular and gene therapies.

Industry activities and milestones supporting the trend for growth in the biopharmaceutical industry include ever more capacity coming online, including many developers and CMOs adding ≤2,000 L single-use bioreactor-based process lines, sometimes multiple run in parallel, and Celltrion (S. Korea) bringing its capacity up to 330,000 L from its current 140,000 L, with this alone significantly increasing industry capacity (see the capacity-related trend discussion). Just among CMOs, this year's *Annual Survey* reports single-use-based commercial scale expansions and new construction at 18 facilities totaling ~150,000 L.

#5 Trend: Products Costs and Price Controls Continue as a Threat

Costs of biopharmaceutical products, along with most other new(er) pharmaceuticals, and related government-imposed price controls continue to be a threat to the industry. Major threats include political imposition of price controls, and products simply being too expensive for individual patients and not being sufficiently covered by insurers due to high costs, with patients essentially forced to use cheaper alternatives or even avoid treatment. To use a worst-case and increasingly common example, a new cellular/gene therapy costing >$.5 million for a course of treatment (with some costing >$1 million), even if 90% covered by insurance (leaving $50,000 for just a 10% 'co-pay' by the patient), is too expensive for most patients to pay themselves.

As industry trade associations and supporters continue to point out, any new price controls, particularly if imposed in the U.S. (still the source for most pharmaceutical R&D, most pharmaceutical sales/revenue, and where most companies are based), will have adverse effects by inhibiting investment in product R&D, clinical trials, manufacturing and marketing. Calls for more industry price regulation are ongoing in the U.S. where politicians from both leading political parties are calling for diverse price controls on pharmaceuticals.

Although not something the (bio)pharmaceutical industry likes to discuss, in many respects, U.S. (bio)pharmaceutical customers to a good extent subsidize prices in most other countries worldwide. U.S. patients and insurers generally pay the most for (bio)pharmaceuticals, the U.S. market remains the largest major (bio)pharmaceuticals market and stands out for its still lacking significant government intervention and control of pharmaceutical costs. If cost controls are imposed in the U.S., this could well disrupt the world's pharmaceutical markets, since costs in other countries would likely need to be commensurately increased (presuming industry, led by U.S.-based companies, continues to invest in innovative products development). In the extreme, imposition of significant cost controls in the U.S. could lead the (bio)pharmaceutical industry to adopt single worldwide pricing, with likely most every country other than the U.S. paying more than it currently does. Whatever the outcome may be, it appears that pharmaceutical costs and government efforts to control them will be among the major issues involved in the Nov. 2020 Presidential and other elections in the U.S.

Biopharmaceuticals with their increased manufacturing complexity and costs, and generally being newer and treating previously untreated or inadequately treatable diseases, tend to be among the most expensive pharmaceutical products. In some cases, e.g., cellular/gene therapies, costs for a course of treatment can be over $1 million. Both biopharmaceutical and drug developers continue to generally follow the pattern of setting prices by charging a discount vs. the total healthcare costs of current options/alternatives, in many respects seeking to charge as much as possible by providing some actual or theoretical cost-savings vs. current alternatives. Price are set, particularly in the U.S., based on what patients and payers will willingly pay, not based on actual costs of development, manufacturing and marketing.

Costs of manufacturing continue to remain just a small portion relative to sales prices/revenue, e.g., a typical monoclonal antibody product generally is estimated to have total costs for manufacturing in the 4-6% of sales prices/revenue, while most cellular and gene therapies generally have manufacturing costs about 2x higher, e.g., in the 10% range.

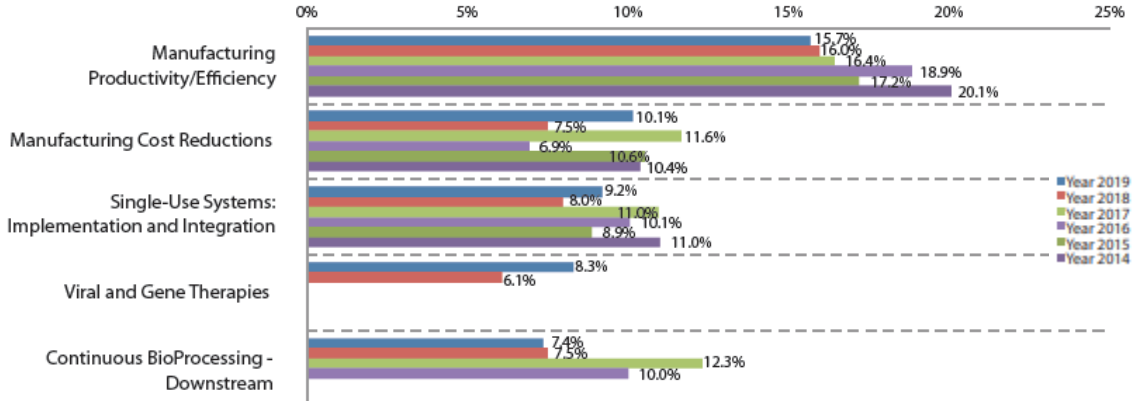
#6 Trend: Manufacturing efficiency/productivity still seen as most important trend

Many of the trends in the bioprocessing industry are being driven by widely perceived needs for improved efficiencies, quality, and cost reductions in manufacturing processes. To remain competitive better ways are needed to:

a) Decrease new products' time-to-market (increase speed-to-market);
b) Streamline new technology testing and adoption processes, make adopting new bioprocessing technologies quicker and less painful; and
c) Decrease commercial manufacturing costs and complexity.

As in prior years, this year when respondents were asked to cite "The SINGLE most important trend or operational area," (Fig 3) the most commonly perceived trend, as indicated by the largest portion of respondents, 15.7%, was "Manufacturing Productivity/Efficiency," with this largely unchanged from 2018,16.0% and 16.4% in 2017. Despite remaining the no. 1 "most important" cited trend in recent years, "Manufacturing Productivity/Efficiency" is showing a trend for reduction, e.g., is down from 20.1% in 2014.

Fig 3: SINGLE Most Important Biomanufacturing Trend or operational area, 2014-2019



Source: 16th Annual Report and Survey Biopharmaceutical Manufacturing Capacity and Production, April 2019, BioPlan Associates, Inc. Rockville MD, www.bioplanassociates.com/16th

Trends Analysis

Rather steady incremental improvements in productivity are common, the general rule, in bioprocessing. Based on survey and other data, BioPlan has reported rather steady increases in bioprocessing productivity, particularly upstream bioprocessing, over the past 30+ years since the first adoption of recombinant technologies.[1,2] This includes documenting rather steady increases in upstream titers from the 1980s to the present, starting at average titer in the 1 or few 10^{ths} of a gram/Liter and now averaging over 3 g/L, an increase of over an order of magnitude.

This year the 2nd-place "most important" trend cited by survey respondents was Manufacturing Cost Reductions", up from 5th place last year. The 3rd and 4th "most important" trends were "Single-use Systems: Implementation and Integration" and "Viral and Gene Therapies," respectively. "Downstream Processing Advances," in 2nd place last year, ranks 7th this year. "Continuous BioProcessing – Downstream" ranked 5th this year.

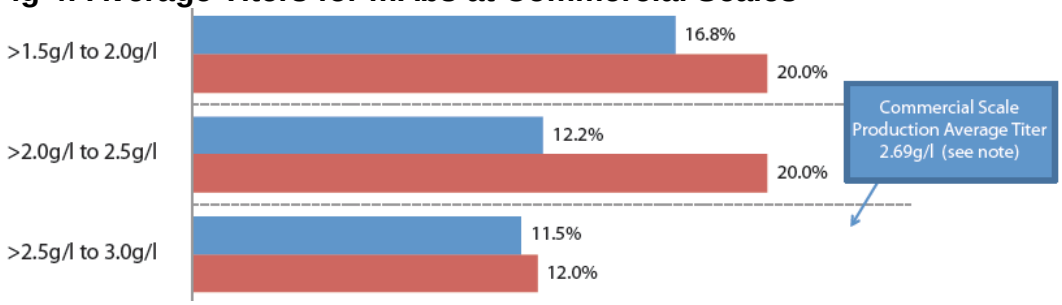
#7 Trend: Bioprocessing Productivity Continues to Increase

Annual survey data and other sources confirm that bioprocessing efficiency and productivity, in terms of upstream titers and downstream yields have and will continue to increase. Related to this, bioprocessing professionals and companies must spend increasing time and effort assessing available technologies and manufacturing options to keep their bioprocessing up-to-date and make sure they are attaining current industry norms, if not optimum levels, for productivity, product quality and lower costs.

Related survey findings this year include:

- The annual growth rather or CAGR for the average titers at commercial and clinical scales from 2008-2019 are very similar, 5.02% for commercial scales and 5.08% for clinical scales (Fig 4).
- The average titer for reported new commercial-scale monoclonal antibody (mAb) upstream bioprocessing was 2.69 g/L, down from 3.20 g/L last year. It can be concluded that the overall average upstream titer with commercial scale mAbs manufacturing is about 3 g/L, with there being wide differences among facilities and processes.
- Overall, the there is a clear trend for incremental increases in commercial scale titers. Nearly all other annual survey data back to 2008 show consistent incremental increases in titers. In related trade periodical articles, including resulting from contacting several 100 more senior bioprocessing professionals associated (e.g., identified from publications, presentations, patents) with commercial biopharmaceutical product and related process development, BioPlan has reported incremental increases in titers over the past 3+ decades.[1,2].
- The average reported titer for late-stage clinical-scale biologics for new mAb bioprocesses) this year is 3.03 g/L, down for 3.20 g/L last year. Clinical production titers show a general trend for incremental increases, e.g., the average clinical scale titer was 1.96 in 2008.

Fig 4: Average Titers for mAbs at Commercial Scales



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#8 Trend: Biosimilars/biogenerics bringing more products and players

Many follow-on products – biosimilars, biogenerics and biobetters - in development and entering world markets indicate the maturation of the biopharmaceutical industry, as its current major blockbuster products and established platform technologies start to go off-patent. Follow-on biopharmaceuticals are a rapidly growing field. Many products are in the development pipeline, with this expected to change biopharmaceutical manufacturing and marketing.[3,4]

The Biosimilars/Biobetters Pipeline Database (www.biosimilarspipeline.com; marketed by BioPlan) now reports 1,064 biosimilars (including biogenerics) in development or marketed worldwide, up from 940 last year, including >600 now in clinical trials or marketed in 1 or more countries. There are also >580 biobetters in development or marketed worldwide, with 362 in clinical trials or marketed. About 800 companies worldwide are involved in follow-on (biosimilar, biobetters and biogenerics) products, with many new entrants in both developed and emerging regions. CMOs are already reporting increased business, about 15% increase in revenue, attributed to biosimilars projects.

There are >680 follow-on currently marketed (somewhere), although ~40% of these are biogenerics manufactured and marketed mostly in developing countries (e.g., not marketable in U.S., EU and other major GMP markets due to inability to meet current standards or lacking sufficiently extensive comparative analytical and clinical testing required to receive approvals in major markets). Most biogenerics are marketed in lesser-and often non-regulated international commerce, in developing countries.

With such a healthy development pipeline, within ≥5 years biosimilars and other new follow-on biopharmaceuticals may outnumber reference and other innovative biopharmaceutical products, even in the U.S. market. This will change the underlying nature of the biopharmaceutical industry. Markets will likely become more competitive and more like generic drugs markets.

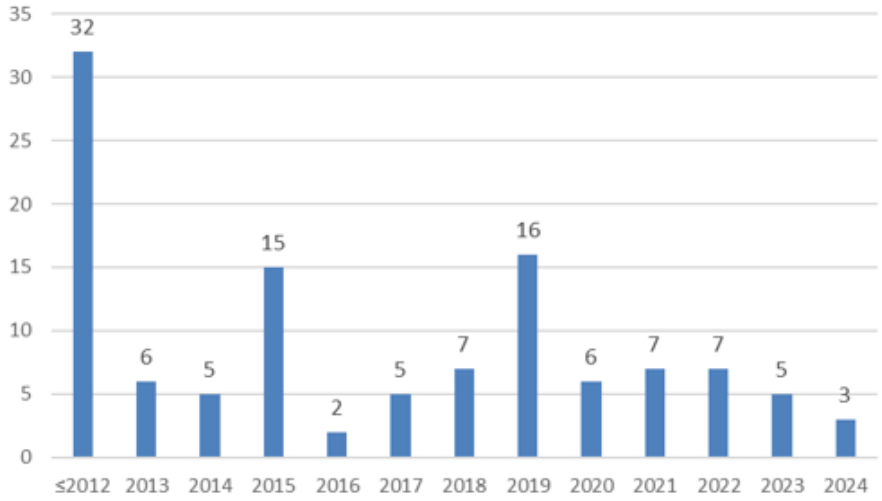
Biosimilars (and biogenerics in lesser- and non-regulated international markets) are resulting in several new players entering the biopharmaceutical industry, and new manufacturing facilities being constructed. The largest number of biosimilars (i.e., major market-targeted biosimilars) in development and their developers remain in the U.S., with the U.S. still the primary location for biopharmaceutical R&D and the largest market for biopharmaceuticals. But Europe, India and China are the other major centers for biosimilars development, including with more marketed products (although mostly

biogenerics rather than products that could receive approvals in major markets as biosimilars) and continue to ramp-up their R&D and product portfolios.

Biosimilars are also affecting the bioprocessing industry and its suppliers' markets. This includes nearly all biosimilar developers using single-use systems as much as possible for manufacturing, including adopting single-use for commercial manufacturing. And as BioPlan has reported, biosimilars involve essentially the same (or rather biosimilar) products competing against each other, their reference products and other products used for the same indications. Marketing will be fiercely competitive, including product costs, and this is forcing developers to adopt optimally efficient bioprocessing technologies. Biosimilar manufacturers, many starting with no biopharmaceutical expertise or infrastructure, are often more receptive to adopting new technologies compared to innovative products developers, mostly well-established large companies, taking more conservative, time-proven approaches and/or preferring to stick with proven in-house platform technologies.[5-7]

Fig 5 below shows the number of reference products (the long-marketed model products for biosimilars) by their estimated U.S. biosimilars marketability date. This is the year in which the reference products come off U.S. market exclusivity, nearly always determined by patent expirations, but also sometimes involving expiration of regulatory-granted exclusivities, including the statutory 12 years of post-BLA marketing exclusivity (no biosimilar version approvals) and 7 years from having received approval with orphan designation. As can be seen, there was essentially a wave of reference products for which biosimilars could be marketed (coming off patent) several years ago and another happening now.

Fig 5: Number of Biosimilars in the U.S. Pipeline by Launchable Dates



Source: 16th Annual Report and Survey Biopharmaceutical Manufacturing Capacity and Production, April 2019, BioPlan Associates, Inc. Rockville MD, www.bioplanassociates.com/16th

Research has shown that the average length of effective U.S. patent protection for reference products after FDA approval is over 15 years. That is, biopharmaceuticals coming to market almost always have 15+ years of effective patent-based protection from biosimilar competition. It is very rare for any biopharmaceutical to now be developed and come to market with less than about 20 years post-approval patent protection. Essentially no biosimilars versions of reference products with any decent-sized markets would enter the U.S. market any earlier even if approvals-based new biologics market exclusivity was significantly reduced or eliminated. Patents will remain what determines U.S. biopharmaceutical product marketability; and efforts by activists and politicians to reduce approval-related exclusivity, if implemented, will not result in biosimilars entering the U.S. market any earlier.

#9 Trend: Bioprocessing bottlenecks persist; continuous processing a needed response

This year, the factor most frequently cited as likely to cause capacity constraints in the next 5 years continued to be “Facility Constraints,” with this remaining the no. 1 cited factor since asking this question in 2008 (Fig 6). Facility constraints were perceived slightly more among respondents as causing bioprocessing bottlenecks this year (52.2%), up slightly from 50.0% last year. This factor was followed by “Analytical testing and drug product release,” 36.4%, with quality-related testing often complex, costly and taking weeks; and “Inability to hire new, experienced technical and production staff,” 28.8%. Overall, 47.5% of respondents reported “Moderate” or more severe current constraints on capacity at their facility.

There is general consensus, or it is common knowledge within the industry that downstream (vs. upstream and fill-finish) operations continue to cause most, including the most severe, bioprocessing constraints (bottlenecks). As noted in other sections, BioPlan has documented rather significant increases over time with industry upstream titers currently (for commercial mAb manufacturing).[1,2] This includes an order of magnitude greater average titers now vs. several decades ago. But at the same time, downstream yields have changed little, from historical ~70% to ~75%. So, downstream bioprocessing needs significant productivity improvements to keep up with constant incremental improvements in upstream processing.

When respondents were asked to identify areas that need to be addressed (e.g., by bioprocessing suppliers) to avoid significant future bottlenecks, the number 1 response was “Develop better continuous Bioprocessing-DOWNSTEAM,” cited by 42.5%, with this also the top-cited ‘need’ in 2018. The 2nd-cited ‘need’ to avoid future bottlenecks, was “Add downstream in-house capacity (process line expansion),” cited by 36.3%. CMO-based respondents cited “Develop better continuous Bioprocessing-DOWNSTEAM” needs more frequently than developer-based respondents, 42.0% vs. 45.5%. “Develop better continuous Bioprocessing-DOWNSTEAM” was cited much more frequently by U.S. vs. Western European respondents, 45.0% and 33.3.%, respectively.

Fig 6: Factors Creating Future Capacity Constraints, in 5 years

Source: 16th Annual Report and Survey Biopharmaceutical Manufacturing Capacity and Production, April 2019, BioPlan Associates, Inc. Rockville MD, www.bioplanassociates.com/16th

Fig 7: Key areas to Address to Avoid Capacity Constraints

Source: 16th Annual Report and Survey Biopharmaceutical Manufacturing Capacity and Production, April 2019, BioPlan Associates, Inc. Rockville MD, www.bioplanassociates.com/16th

Chromatography columns remain overall the top-cited downstream (and overall number 1) bioprocessing problem area. This included 62.9% of respondents, up from 57.4% last year and 48.3% before that, citing “Chromatography columns” as causing “Moderate constraints” or “worse” constraints; and 61.9% citing “Chromatography columns” as causing them any constraints. “Depth filtration,” another downstream process, came in 2nd this and last year as the most commonly cited cause of bioprocessing constraints.

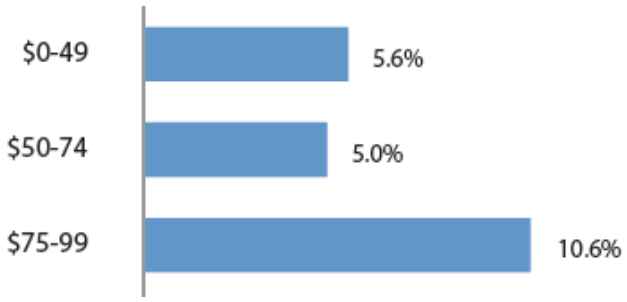
#10 Trend: Industry seeks lower manufacturing costs

The bioprocessing industry continues to recognize that success in biopharmaceuticals requires the ability to cost effectively manufacture commercial-scale products. This year, again, most respondents continue to report that their facility has implemented programs to reduce bioprocessing costs. A majority, 53.2%, reported having "Implemented programs to reduce operating costs" within the past 12 months. The 2nd most commonly cited cost reduction activity in the past year was "Reduced process development times and costs," at 34.1%. Note, it is presumed that the great majority of respondents only considered API manufacturing, and did not include formulation, fill-finish, packaging and other downstream product manufacturing costs.

Working to reduce bioprocessing costs has become a routine activity with most facilities. Besides biosimilars and other new product entries increasing competition, other forces are increasing the need to cost-efficiently manufacture products. Pressures for lower costs include high pharmaceutical prices, threats of cost controls, and discounting of biosimilars, with most expected to sell at ~30% discounts relative to reference products in the U.S. market.

This is the first year we surveyed regarding average cost/gram for recombinant protein manufacture. The average reported cost was $364.06/gram, up from $306.8/g last year, for respondents' primary recombinant protein product, usually a monoclonal antibody.[7] Somewhat surprising, 21.2% of respondents reported an average cost of <$100/gram for their facility. These lowest costs are generally associated with the very largest 100,000+ L facilities that have long been paid for; and newer super-sized facilities, e.g., Samsung and Celltrion in S. Korea. A slightly smaller percentage, 15.6%, up from 13.9% last year, reported cost/gram >$1000. These data were reported by the surveyed bioprocessing professionals, not financial staff or top corporate executives. Estimations of manufacturing-related costs may differ from depending on who reports the data, such as whether the costs of capital invested are included.

Fig 8: AVERAGE cost/gram for Recombinant Protein manufacture



Source: 16th Annual Report and Survey Biopharmaceutical Manufacturing Capacity and Production, April 2019, BioPlan Associates, Inc. Rockville MD, www.bioplanassociates.com/16th

Hundreds of dollars per gram may sound high for recombinant protein manufacture at commercial scales. But even considering dosages on the high side, e.g., a monoclonal antibody dosed at 100 mg/dose (1/10th gram), allowing for a higher-end cost of each gram used to manufacture make just 10 doses, and presuming costs of $1,000-$10,000/dose, each gram can provide $10,000-$100,000 in revenue. This is a 1/270 to 1/27 ratio of bioprocessing costs to sales revenue. Even at the higher-end 1/27 ratio, the cost of manufacture is 3.7% relative to revenue. BioPlan generally presumes that total biopharmaceutical product manufacturing costs, including fill-finish processing and all supporting facility infrastructure, is in the range of 4%-6% for mainstream proteins/mAbs.

#11 Trend: Bioprocessing budgets continue to increase

Survey results continue to show that companies are investing more in biopharmaceutical R&D and production, including hiring staff and expanding manufacturing capacity. Budgets for new capital equipment continued to be an area of significant growth, with respondents reporting an average increase of 7.9%, down from 8.2% last year, in facility bioprocessing budgets for 2019. The highest budget increases were rather consistently reported in 2017, with an apparent trend for decreasing budget increases in the recent years.

Much of this budget growth involves construction of new facilities, retrofitting, and addition of capacity at existing facilities, with this increasingly single-use based. This is a change from about 10 and more years ago when bioprocessing budgets showed decreases in key areas ranging from outsourcing production, hiring new scientific staff, to new facility construction. These widespread reductions, mostly associated with the prior worldwide economic downturn, have passed; and respondents have been and continue to indicate that their bioprocessing-related budgets are now continuing to increase annually. The area with the lowest projected budget growth, 2.6%, but still growing, was outsourced biopharmaceutical manufacturing.

It is very significant that this year no budget decreases were reported in any of the areas surveyed, confirming an overall increase in bioprocessing budgets among developer companies. Suppliers/vendors are reporting that sales revenue continues to increase, with many of the largest suppliers regularly reporting annual increases of 12%-15%+.

Fig 9: Approximate Average Change in Biomanufacturers' Budgets for 2018

Source: 16th Annual Report and Survey Biopharmaceutical Manufacturing Capacity and Production, April 2019, BioPlan Associates, Inc. Rockville MD, www.bioplanassociates.com/16th

#12 Trend: Single-use systems use still growing

Single-use equipment continues to make advances into biopharmaceutical manufacturing, and is becoming increasingly common in most areas, particularly at pre-commercial scales (e.g., clinical and preclinical) where single-use systems dominate stainless steel systems, especially upstream. BioPlan estimates that ≥85% of pre-commercial (R&D and clinical) product manufacturing now involves considerable, if not near total, single-use systems-based manufacturing, particularly upstream manufacturing. Single-use systems adoption will increase as more new products now being developed using single-use systems move through the development pipeline to clinical scale manufacturing and on to cGMP commercial production using single-use systems.

Again, this year over 80% of respondents reported current considerable use of single-use bioprocessing equipment. The use of "Disposable filter cartridges" was the most frequently cited product class, cited by 85.6%, followed by 84.5% reporting use of "Bags, empty," e.g., storage, bioreactor and mixer bags. In terms of major equipment indicative of a fully or substantially single-use-based facility, over 3/4 (79.9%) reported use of single-use bioreactors, with nearly one-half (46.5%) reporting any use of perfusion bioreactors.

Reported annual growth (adoption) rates in single-use systems usage, in terms of their first usage within the facility (not growth in revenue) was highest, 11.5%, for Membrane adsorbers," followed by "Mixing systems" at 10.9%. "Perfusion devices" adoption was reported at 9.2%.

Fig 10: Usage of Disposables in Biopharmaceutical manufacturing, any Stage of R&D or Manufacture

Source: 16th Annual Report and Survey Biopharmaceutical Manufacturing Capacity and Production, April 2019, BioPlan Associates, Inc. Rockville MD, www.bioplanassociates.com/16th

#13 Trend: Continuous bioprocessing in demand, seen as needed

This year when asked what bioprocessing *innovations* are most needed, respondents continue to very frequently cite aspects of continuous bioprocessing. This is besides continuous bioprocessing downstream reported at the primary 'need' to address current bioprocessing bottlenecks.

This year the most frequently cited downstream technology being considered for adoption was "Continuous purification systems," 33.6%, followed by "Membrane technology," 28.9%, with this no 2 last year and no 3 the year before. And this year "Continuous bioprocessing downstream (chromatography)" was cited by 41.1%. When asked to identify the top areas where suppliers should focus their development efforts, the most cited was "Continuous bioprocessing downstream (chromatography)" at 43.8%, followed by "Disposable/Single-use: Purification," 41.1%. The frequency of citation of other areas was much lower.

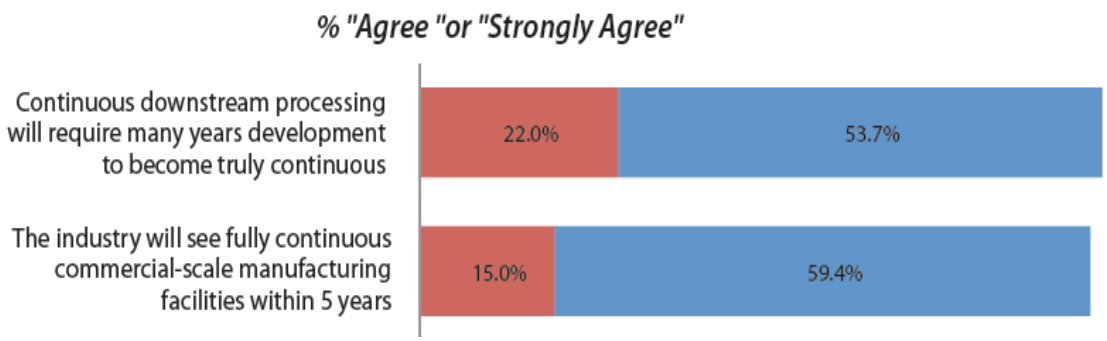
Continuous bioprocessing is the area in which the largest portion of bioprocessing professionals see need for improvements to resolve downstream problems, including difficulties keeping up with increasingly efficient upstream processing. Continuous bioprocessing is often cited in responses to other questions as an option for resolution of bioprocessing problems and continues to be a major area for optimism. Hopes are increasing that these systems will become available and adoptable for mainstream bioprocessing, including GMP commercial manufacturing.

Upstream perfusion has been around for decades, even available in single-use formats; downstream bioprocessing, while on the other hand, continuous chromatography systems are just starting to enter the market. Perfusion at larger scales has remained mostly limited to use of stainless steel equipment and mostly only adopted at commercial scales by a small core of well-established major facilities often now having used it for decades, such as for manufacture of recombinant Factor VIII and other sensitive proteins. There is a trend for increased adoption of perfusion for early and even mid-phase clinical supply needs, but with manufacturing often redesigned for fed-batch production at commercial scales. BioPlan expects to see fully continuous processing at commercial scales, including using single-use systems, in the next 5-10 years.

In terms of upstream perfusion, the most advanced part of continuous bioprocessing, the survey continues to show that bioprocessing professionals have lingering doubts, with this conflicting with respondents often citing continuous processing as expected to resolve problems with bioprocessing (as reported in another trend section); and

responses concerning desires and expectations for availability of continuous processing. This includes this year, as shown below, over 3/4s (75.7%) of respondents “Agreeing” or “Strongly Agreeing” that “Continuous downstream processing will require many years development to become truly continuous.” And nearly the same, 74.4%, reported “Agreeing” or “Strongly Agreeing” that “Industry will see fully continuous commercial-scale bioprocessing facilities within 5 years.” So, there are both significant doubts and hopes regarding industry adoption of continuous bioprocessing.

Fig 11: Concerns Over Perfusion Processes vs. Batch-fed Processes in Bioprocessing



Source: 16th Annual Report and Survey Biopharmaceutical Manufacturing Capacity and Production, April 2019, BioPlan Associates, Inc. Rockville MD , www.bioplanassociates.com/16th

#14 Trend: Bioprocessing capacity growing; cell therapy capacity shortages exist

BioPlan's *Top 1000 Global Biopharmaceuticals Facilities Index* (free database at www.Top1000Bio.com) reports and ranks the top 1,000+ biopharmaceutical manufacturing (bioprocessing) facilities worldwide in terms of known or estimated cumulative bioreactor capacity, along with employment, number of products manufactured commercially and other facility and bioprocessing-related data. The database now tracks over 16.6 million L of production capacity at over 1,550 facilities worldwide, including for manufacture of recombinant and non-recombinant biopharmaceuticals, vaccines and blood/plasma-derived products. An overall breakdown of worldwide bioprocessing capacity is presented in Table 2. Over 825 facilities worldwide now each have ≥1,000 bioprocessing capacity, and over 1,050 have ≥500 L capacity. Worldwide capacity distribution is shown in the following Table.

Table 2: Worldwide Distribution of Bioprocessing Capacity

Region	Capacity (million L)	% Worldwide Capacity	Facilities
U.S./Canada	5.5	33%	566
W. Europe	5.5	33%	389
Japan/Other Asia	2.2	13%	147
China	1.2	7.2%	210
India	1.0	6.0%	108
E. Europe/Russia	0.57	3.4%	61
Middle East/Asia	0.21	1.3%	34
Africa	0.06	0.4%	15
Total	**16.6 million L**	**100.0%**	**1,567**

Factors and trends affecting the amount and distribution of capacity include: single-use process lines making adding capacity relatively quick and simple; ample capacity is available, particularly among largest (multiple >10,000 L bioreactors) facilities; titers and yields continue to incrementally improve, allowing smaller process lines and facilities; and continued investments in new facilities worldwide. Much new capacity, both new facilities and expansions of existing plants, is being added worldwide. Capacity growth is presumed to largely match the overall annual growth rate of ≥12% seen in most other aspects of the industry, including annual biopharmaceutical revenue, number of marketed products, and the bioprocessing supplies and CMO markets.

There currently is no ongoing bioprocessing "capacity crunch," nor is any expected to affect mainstream bioprocessing. There is a definite trend for reduction in expectation of facility capacity shortfalls. This year, only 5.4% of survey respondents reported expecting their facility to experience production capacity "severe constraints" with commercial manufacturing in the next 5 years. The percentages reporting expecting "severe constraints" with later stage/Phase III and early-mid/Phase I-II clinical manufacturing

were even lower, 2.5% and 0.6%, respectively. However, nearly all facilities expect to experience some capacity constraints in the next 5 years, e.g., with only 12.5% of respondents expecting “No constraints” with their facility’s commercial manufacturing

New bioprocessing facilities construction and expansions continue in major markets, and growth in capacity involving commercial scale stainless steel continues, much of this driven by new ‘super-sized’ facilities, such as those of Samsung. But overall the fastest growth (but from low baselines) is in Asia, particularly China.[9] This includes growth in contract manufacturing organization (CMO) capacity growth in China, especially as regulations are changing allowing 3rd parties to manufacture biopharmaceutical supplies. New and expanded Chinese facilities are often adopting state-of-the-art and other advanced bioprocessing technologies. Chinese companies, often with loans and grants from the central and/or local governments, are orienting themselves to be major players in GMP manufacturing on a global scale, including innovative products development and manufacturing. China and India are often compared, with China having now moved ahead of India is terms of capacity and number of facilities, although the average facility size is significantly smaller. The largest Chinese facility still has <80,000 L capacity, rather small by blockbuster biopharmaceutical, particularly antibody, manufacturing standards. China will obviously need to greatly expand its manufacturing capacity to begin to meet the demands of its large domestic population, besides plans to be a major exporter of biopharmaceutical, including to major markets. Much of India’s biologics capacity involves larger vaccines vs. recombinant protein/mAb facilities.

However, there is a worsening ‘capacity crunch’ affecting cellular and gene therapies manufacturing, with these areas and related product demand growing much faster than capacity, with current manufacturing capacity at a severe and increasing deficit. BioPlan conservatively estimates that 5x (500%) current cellular/gene therapy capacity could and would be in use currently if it existed.[8] And in 5 years, 50x or 5,000% more vs. current capacity will be needed to support projected manufacturing needs. BioPlan studies also have shown that nearly 90% of cellular/gene therapy developers would prefer to manufacture using CMOs, but most are not finding the needed expertise and/or facilities among CMOs. This includes an average current ≥18 months wait time to get new projects started. Related to this, there is a trend for cellular/gene therapy developers to increasingly build their own in-house manufacturing capacity, rather than follow their preferences to use CMOs. This is besides many CMOs and CROs currently expanding their cellular/gene therapies capabilities and manufacturing capacity. Shortages of staff with actual training, experience and expertise in cellular and gene therapies manufacturing, particularly at GMP, are already severe and will continue to worsen.

#15 Trend: Hiring in bioprocessing a continuing problem

Hiring of bioprocessing professionals continues to remain a problem area and will likely only get worse in coming years. Problems involve replacing many of the most experienced and senior staff, the baby-boomers starting to retire, and a related shortage of available experienced bioprocessing professionals. Staff are needed for new facilities, and experienced staff are needed in new areas, such as biosimilars, cell and gene therapies; and the industry continues to expand, including new facilities in major markets and developing markets, notably China and other Asian markets.

Concerns and problems with staffing are troublesome particularly concerning process development staff. As in prior years, hiring of process development professionals, continues to be the most commonly cited area in which facilities are reporting difficulty filling positions. “Process development staff, downstream” was the number 1 most difficult to fill area this year, cited by 45.1%. “Process development staff, upstream” came in close at 41.8% this year. “Process development, formulation” moved up to 3rd place this year, at 37.9%.

Facilities in Western Europe are reporting more serious hiring difficulties than in the U.S. Among Western Europe respondents, 57.5% reported difficulties in hiring downstream process development staff, compared to 41.0% for U.S. respondents. Similarly, process development upstream staff hiring difficulties were reported by 55,0% of Western European and 39.8% of U.S. respondents.

Finding bioprocessing and cell culture process specialists with high levels of expertise has always been a challenge; and, despite continued demand and even shortages, no major training initiatives or changes appear to be occurring. The difficulties in hiring may well reflect more facilities seeking to hiring relatively more highly-qualified employees. The experience levels required appear to overall be increasing, as bioprocessing, quality assurance, regulations, etc., only ever become more complex.

Fig 12: Areas Where Hiring Difficulties Exist in Biopharmaceutical Operations

Source: 16th Annual Report and Survey Biopharmaceutical Manufacturing Capacity and Production, April 2019, BioPlan Associates, Inc. Rockville MD, www.bioplanassociates.com/16th

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