BioPlan associates, inc.

TOP 15 TRENDS IN BIOPHARMACEUTICAL MANUFACTURING, 2020

Current Major Trends Affecting Biopharmaceutical Manufacturing:

Summarized from the
17th Annual Report and Summary of Biopharmaceutical Manufacturing Capacity and Production

APRIL 2020

Abstract: This presentation of the Top 15 Trends in Biopharmaceutical Manufacturing (bioprocessing) provides top-level trends information primarily from the 17h Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, April 2020, published by BioPlan Associates (1). This is the most extensive and longest-running annual survey of bioprocessing professionals. We have drawn these insights and 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 further information, To order the full report visit **www.bioplanassociates.com/17th**

INTRODUCTION

In this review we summarize just a few of the 550 pages of data and findings presented in the 2020 17th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production (the "Annual Survey") (see www.bioplanassociates.com/17th).

The biopharmaceutical industry continues to grow in size, breadth, including internationally, and diversity. This now includes industry adapting to recovery from the Covid-19 pandemic, including expected significant expansion of bioprocessing activities worldwide. This is in addition to many new areas moving into the mainstream, e.g., cellular and gene therapies and antibody-drug conjugates (ADCs) as therapeutics.

As part of our annual analyses of biomanufacturing (bioprocessing), this, our 17th year, we again surveyed over 130 decision-makers within bioprocessing organizations, both developer and contract manufacturing organizations (CMOs), involved in bioprocessing activities in 33 countries. To assess industry growth and challenges from suppliers' perspectives, we also surveyed 150 industry supplier/vendor respondents.

The Annual Survey includes quantitatively evaluating the current industry situation, trends, and where these are going. This summary provides insights into selected broad trends, including those affecting:

- Industry size, growth, number of products, etc.
- Demands for increased efficiency, productivity
- International biomanufacturing, off-shoring, etc.
- Cell and gene therapies and other new(er) areas
- Single-use vs. stainless steel-based processing

Overall, the pharmaceutical industry and its and biopharmaceutical subset remain active, growing, and profitable. This very top-level finding has now been reported in the annual survey publication for 17 years, with the industry (in terms of revenue and nearly every other parameter) continuing to grow consistently at ~12% - 13% 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 (i.e., with active agents manufactured using biotechnology/living organisms). A significant portion, now >1,650 products, in the development pipeline are follow-on biopharmaceuticals, mostly biosimilars (≥1,100; here including 'biogenerics') and biobetters (≥550) (see the Biosimilars/Biobetters Pipeline Directory, www.biosimilarspipeline.com, marketed by BioPlan).

OVERVIEW OF TRENDS IN BIOPHARMACEUTICAL MANUFACTURING (Bioprocessing)

The biopharmaceutical industry has continued to grow, evolve and diversify over the past 40 years. This has demanded new and improved bioprocessing technologies to meet product demand, reduce costs, increase efficiencies, and comply with safety and regulatory requirements. This has led to improvements in productivity as the industry's processing and development pipelines have matured. Many of the largest pharmaceutical companies today are devoting increasing their development efforts to include more biopharmaceuticals rather than small molecule drugs.

Multiple sources continue to report that most of the current major pharmaceutical companies, including Big Pharma companies, are spending 40%-50% of their R&D on biopharmaceuticals development, with this percentage slowly increasing. Many traditional drug (chemically-manufactured active agent products) companies are now putting most of their R&D into biopharmaceuticals. And there continues to be a strong component of smaller, mostly newer and innovative biopharmaceutical developer companies. Further, according to our Top1000bio.com analysis and website, over the past 12 years we have seen increasing concentrations of bioprocessing in certain developing regions, not just major market countries.

Incremental innovations in improved manufacturing productivity continue, exemplified by multiple decades rather steady increases in average upstream titers (discussed as a trend below). Other innovations also speed discovery, bioprocessing, 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 Covid-19 and other pandemic and biodefense, biosimilars, cellular and gene therapies, and many other new opportunities in both established and emerging markets.

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

- Biological products, often each with smaller markets, including more orphan and even personalized products.
- Bioprocessing facilities worldwide, especially in major markets and Asia. This now includes an upcoming wave of facilities coming online for Covid-19 and other pandemic and biodefense products development and manufacturing.

- 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
- Adoption of single-use systems for commercial production, often involving scaling-out with multiple 1,000-2,000 bioreactors
- Adoption of continuous processing, including upstream perfusion and continuous chromatography for downstream processing, as these become more mainstream, including adoption for commercial manufacturing, in coming years
- Efficiency and productivity in bioprocessing as titers and yields continue to incrementally increase
- 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, PAT, etc., including more of this 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, CRISPR and other genetic engineering advances
- Complex regulations, which drive many other specific needs and advances

The 15 major trends driving such changes in the biopharmaceutical industry are discussed below. We note that these are not presented in any particular order. And, in fact, many of the trends tend to be interdependent. Such as the increase in adoption of single-use devices, requiring greater automation, but allowing greater flexibility and modularity in bioprocessing. This is one example of the integration of trends that are permitting greater expansion and regionalization of bioprocessing.

TRENDS Analysis

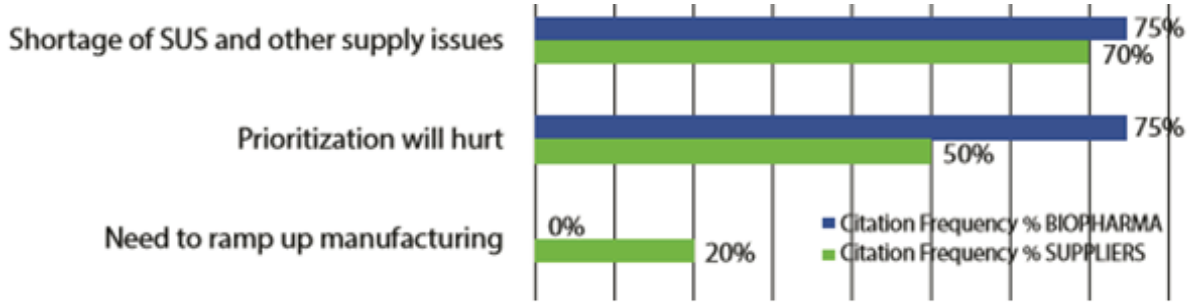
1 TREND:

Biopharma Industry has quickly adapted to the Covid-19 pandemic

We researched the impact of the Covid-19 pandemic in a supplemental study to identify temporary and permanent changes and trends resulting from the pandemic. Results are included in the 17th Annual Survey publication. To capture these insights, in late May 2020 BioPlan interviewed 21 executives at biopharmaceutical developers and bioprocessing suppliers.

Some of the key current fears and related resolutions/plans expressed by interviewees are shown below. By far, the most serious immediate fears were "Shortage of SUS and other supply issues," concern about inability to obtain needed single-use supplies in a timely manner, and that "Prioritization will hurt." [non-Covid-19 projects] as they prioritize their orders and activities, pushing pandemic/biodefense-related to the front of the line. This prioritization combined with expected worsening of ongoing single-use supplies shortages (already causing long lead/wait times to get orders filled) will result in many facilities being losers and other being winners in terms of suppliers, both of equipment and CMO services, responding to inquiries and filling orders. The incidence (%) of biopharmaceutical companies having concerns ('fears') regarding shortages and prioritization is higher among biopharmaceutical companies vs. suppliers.

Fig 1: Top-level Near-term Fears Due to the Covid-19 Pandemic



The operational aspects of the biopharmaceutical industry and its bioprocessing sector have rapidly pivoted and adapted to the Covid-19 pandemic. While many other industries continue to struggle with their adaptation to the pandemic, the biopharmaceutical industry and its manufacturing (bioprocessing) sector have, in most respects, already well adapted, with most expected major changes already implemented and working well (enough). The pandemic's first wave had begun to stabilize in many regions (Summer 2020) and near-term responses

to actually dealing with the pandemic have generally been effective. The most significant and long-term trends and effects on bioprocessing will be associated with the coming years-long worldwide recovery and related industry responses to pandemics (discussed in the next trend section), not adaptation to the pandemic itself.

There is now generally more biopharmaceutical R&D and manufacturing being started or planned at many bioprocessing facilities/companies due to the pandemic. This includes unprecedented rapid worldwide expansions of R&D and bioprocessing capacity at a good number of facilities, mostly for manufacture of pandemic and biodefense vaccines and therapeutics. These activities involving expanded pandemic R&D or manufacturing, are in some cases pushing or displacing other bioprocessing to other facilities. That is, pandemic response is mostly adding R&D and manufacturing to facilities, yet generally not halting other ongoing activities; although many could be giving lower priority. For example, even smaller contract manufacturing organizations that are not involved in pandemic-related R&D or manufacturing are starting to see increased new projects and future demand, as non-pandemic/biodefense projects are shifted from developers to CMOs, or from one CMO to another.

Near term responses, which could be considered short-term trends, include:

- Biopharmaceutical R&D and bioprocessing facilities worldwide are now considered 'essential' by most countries.
- Nearly all bioprocessing facilities are continuing their work throughout the initial wave of the pandemic without much, if any, interruption. In fact, many have or are ramping-up their R&D and manufacturing.
- Most facilities have or expect to increase their R&D and bioprocessing, whether pandemic-related or often due to displacement of non-pandemic projects by pandemic projects at other facilities.
- Major changes in personnel management and facilities operations have been associated with the need for social istancing. Facilities have universally imposed social distancing of staff, often including isolating groups of workers, such as R&D and different shift staff. from others within the facility; only a few at a time working within labs. or manufacturing suites; no overlapping of staff working different shifts, etc. R&D and bioprocessing staff are, like other staff, working from home as much as possible.
- More attention is being paid to assuring the robustness of supply chains and maintaining sufficient supplies in-house. This includes many facilities increasing the amount of supplies they maintain in-house, such as now holding 12-18 months' worth of supplies in storage vs. previously only maintaining 6-12 months' supply.

Between the ramp-up in bioprocessing activities and facilities moving to buy and hold more supplies in-house, shortages and lead/wait times are getting worse, most noticeable with single-use supplies

Among bioprocessing equipment and technology suppliers, nearly all are seeing near-term increased orders and expect even more increase in the future, primarily due to companies/facilities rapidly advancing pandemic/biodefense-related R&D and manufacturing. As a result, many suppliers' manufacturing facilities have added shifts or even moved to 24/7 manufacturing. Increases in current and expected orders include single-use supplies, with pandemic-related increases in bioprocessing expected to further worsen ongoing shortages of key single-use products, often attributable to shortages of high-purity polymers. Most bioprocessing suppliers are also reporting near-term increases in sales.

Facilities have universally imposed social distancing of staff, often including isolating groups of workers (from others, within the facility), such as only a few at a time working within labs. or manufacturing suites. Many lesser-essential staff, particularly those not performing or planning R&D or manufacturing work mostly or even fully from home. The industry rather quickly and rapidly made such needed changes in staff management and related facilities' operations, with most of this now implemented, no longer novel, perhaps no longer to be considered much of a new trend.

Related resolutions or considerations cited included:

- **"Need to ramp up manufacturing,"** with many pandemic-related projects starting or being rapidly advanced by end-users, and with more and larger orders coming in and expected by suppliers.
- **"Ramp up investment in pandemic preparedness,"** with many supplier product manufacturing facilities already adding new and expanding pandemic product-related R&D and manufacturing, including facilities expansions and adding more daily work shifts.
- **"Need for collaboration,"** with supplier executives now seeing more need to share information and collaborate among themselves and also more with their customers. Collaboration may have to include some high-level coordination of suppliers' responses supply chains to better assure avoidance of both shortages and excesses, including under- and over-investment in expansions in certain areas. Access to raw materials, such as some high-purity polymers for manufacture of single-use products, may need to be coordinated among manufacturers.

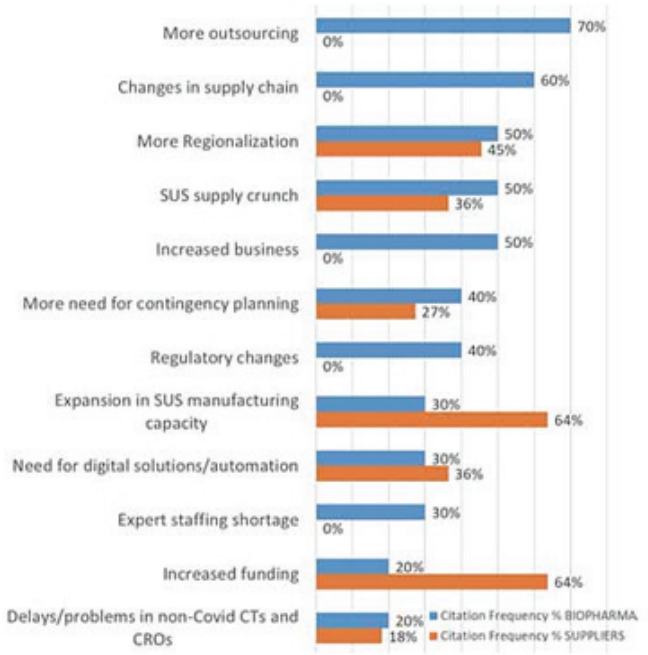
2 TREND:

Longer-term Industry Responses to the Pandemic Will Bring Many Changes

The major changes affecting the biopharmaceutical industry and bioprocessing have yet to come, as the industry settles in and responds to the pandemic. This includes managing an expected 10s of $billions in funding for pandemic- and biodefense-related vaccines and therapeutics R&D and manufacturing. Billions of doses of vaccines are to be produced annually, in addition to pre-pandemic product manufacturing. The biopharmaceutical industry and its bioprocessing sector have already adapted relatively well to the ongoing Covid-1 pandemic, with the major near-term changes including a general increase in R&D, and bioprocessing and supplier manufacturing activities, and supply chain security. The big changes will come as the industry adapts to resolving the Covid-19 pandemic, and to address the potential for future pandemics.

Developer and supplier company executive interviewees' top-level responses when asked to cite the major long-term effects of the Covid-19 pandemic on the bioprocessing sector are summarized in the Figure below.

Fig 2: Long-term Effects of Covid-19 on Bioprocessing



Biopharmaceutical company executives' top ranked expectations for long-term effects, those cited by ≥50% of respondents, were:

- "More outsourcing," with 70% of developer interviewees citing this
- "Changes in supply chains," with 60% of developer interviewees citing this, including more concerns about and involvement with suppliers, and securing '2nd sources'
- "More regionalization," cited by 50% of developer and 46% supplier interviewees. This refer to more manufacturing facilities, both developers' and suppliers', being located in more countries, often domestically.
- "SUS supply crunch," cited by 50% of developers and 35% of suppliers, including worsening of current shortages

Overall, the major long-term response to the pandemic will be an expansion of biopharmaceutical R&D and manufacturing activities worldwide, including rapid development and annual distribution of billions of doses of Covid-19 vaccines in the coming years.

Various facilities/companies are already planning investments of $billions to gear-up for pandemic vaccines and therapeutics manufacturing, including rapidly building new and expanding current production facilities. This is often being done 'at risk,' such as building new manufacturing facilities even before any trials start. Much of this bioprocessing sector expansion will be financed by governments and/or philanthropies, such as Gates' family and Wellcome foundations/trusts.

CMOs are and will be affected by the addition of pandemic-related R&D and manufacturing. Most every vaccines-capable CMO facility already has long delays to start new projects, and new high priority pandemic-related CMO projects are pushing out or causing delays at CMOs for many new and planned non-pandemic-associated projects.

Bioprocessing suppliers giving priority to anything pandemic- or biodefense-related is already part of the new post-pandemic reality. Bioprocessing equipment and services suppliers, including CMOs, have nearly all already implemented policies giving higher priority to projects that are pandemic response-related. Those new orders and projects coming in that are not pandemic-related get lower priority, or start later than would have been expected prior to the pandemic.

3 TREND:

Manufacturing Productivity Still Most Important Trend

Many of the trends in the bioprocessing industry are being driven by continued desires and perceived needs for improved productivity, quality, and cost reductions in manufacturing processes. To remain competitive, the industry continues to seek better ways to:

a) Decrease new products' time-to-market (increase speed-to-market).

b) Decrease commercial manufacturing costs and complexity

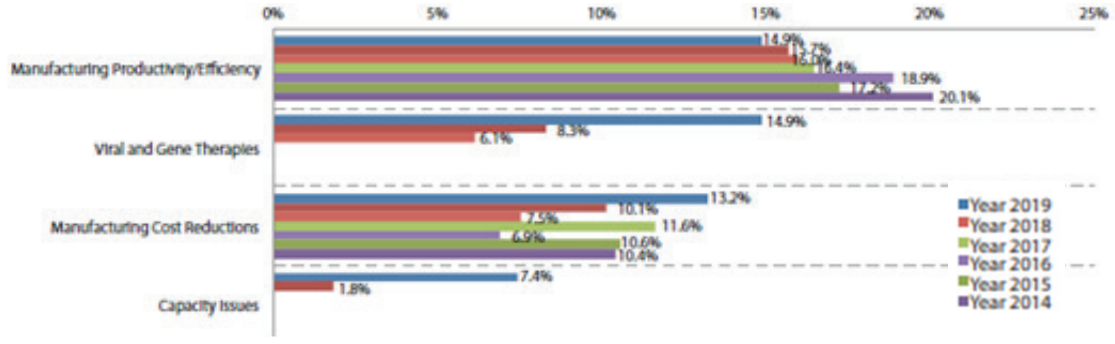
c) Intensify processing, including increasing titers and yields, adopting more flexible bioprocessing, facilities/process lines with small footprints, etc.

d) Streamline new technology, equipment and services testing and adoption processes, make adopting new bioprocessing technologies and manufacturing options quicker and with less pain and costs.

e) Increase clinical and commercial manufacturing output

The most common responses selected when asked to cite "The SINGLE most important trend or operational area," are show in the Figure below.

Fig 3: "Selected" SINGLE Most Important Biomanufacturing Trend or Operational Area, 2014-2020



The most commonly cited trend, as indicated by the largest portion of survey respondents this year, 14.9%, was "Manufacturing Productivity/Efficiency," with this remaining top-ranked for many years. In the #2 spot, "Viral and Gene Therapies," a relatively new area, replaced "Manufacturing Cost Reductions" (now ranked 3rd).

4 TREND:

Mammalian Systems Continue to Dominate

Mammalian cell culture continues to dominate biopharmaceutical development and manufacturing, with this reflected in survey data, as shown in Table 1 below.

Table 1 Areas of Biopharmaceutical Manufacturing Operations

Answer Options	Year 2020	Year 2019	Year 2018
Mammalian cell culture	77.2%	74.2%	79.3%
Microbial Fermentation	37.7%	43.5%	47.8%
Cell Therapy	14.4%	20.6%	17.2%
Yeasi	11.4%	12.4%	16.7%
Gene Therapy	20.4%	18.7%	14.8%
Insect Cells	6.0%	10.0%	3.9%
Plant Cells	2.4%	9.1%	3.4%

This includes use of mammalian cell culture now reported as used by 77.2% of respondents. Mammalian expression systems (cell lines, vectors and associated genetic engineering) continue to be preferred over other options, e.g., microbial and plant systems, particularly for recombinant proteins and monoclonal antibody (mAbs) production. This 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. Preferences for standardizing and minimizing the number of platforms used within a facility or company can be rather strong. This even includes mammalian manufacture of products at early stages for which later-stage development and commercial manufacturing will involve switching to microbial or other non-mammalian bioprocessing.

Overall, use microbial fermentation is tending to decrease. This includes over 1/3 of respondents' facilities now involved with cellular (14.4%) and/or gene therapies (20.4%). The percentage of facilities with yeast-based bioprocessing continues to incrementally decrease, with this now 11.4%, down from 29.9% in 2007.

mAbs remain the single dominant class of biopharmaceuticals in development and world markets, 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, for mAbs and other recombinant proteins and now also for AAV and other gene therapy viral vectors manufacturing.

However, keep in mind that 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.

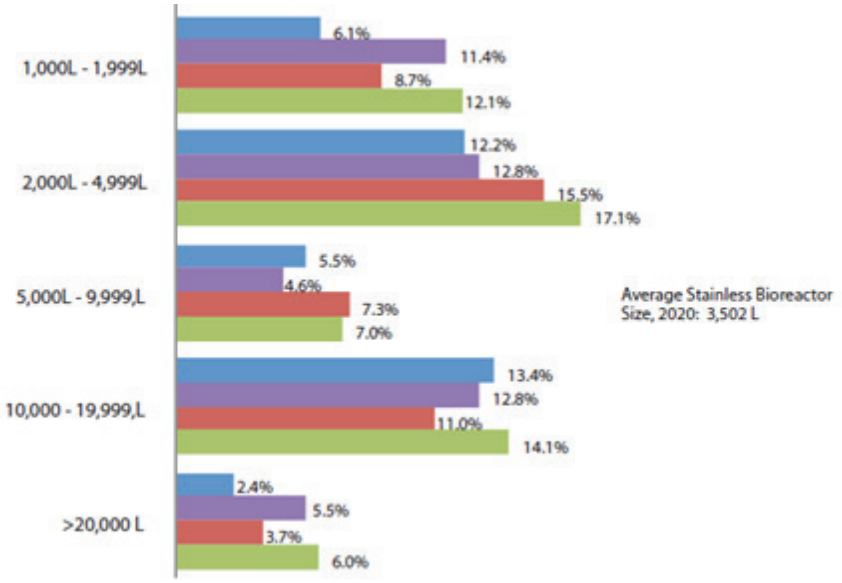
5 TREND:

Stainless Steel Bioreactors: Smaller Installations

Besides fewer new stainless steel bioreactors being installed, with more single-use facilities coming online vs. stainless steel-based ones, a trend is continuing for reduction in volume of steel bioreactors in operation at facilities, as exemplified by the largest size stainless bioreactor onsite. There has been a trend for overall decrease in the percent of respondents reporting their facilities have bioreactors ≥2,000 L, with 2,000 L generally the current cut-off for use of single-use bioreactors. Essentially all bioreactors >2,000 L can be assumed to be stainless steel. One company is marketing larger, e.g., 4,000 L, single-use bioreactors, but reportedly adoption at global worldwide of these larger units are, for the present, somewhat limited.

When asked to cite the capacity of the largest stainless steel bioreactor onsite, the average size (among those reporting having stainless steel capacity) was 3,502 L (similar to the 3,694 L reported in 2018). Nearly every 'largest' onsite steel bioreactor size range has shown an overall decrease in recent years. The number and proportion of facilities with their largest stainless steel bioreactor being <1,000 L has been increasing and is now 38%.

Fig 4: Largest Stainless Steel Bioreactor in Use at Facility, 2020



For comparison, the average reported size of the largest single-use bioreactor onsite was under 25% of the average largest-size onsite stainless steel bioreactor.

Stainless steel bioreactors remain favored for many applications, particularly commercial manufacturing where it often remains more cost-effective to invest in product manufacturing-dedicated facilities anchored by recyclable stainless steel bioreactors and all the associated infrastructure. In sharp contrast, single-use bioreactors now extensively dominate use for R&D and early-phase clinical manufacturing, with an estimated ≥85% of pre- and clinical bioprocessing using single-use systems.

6 TREND:

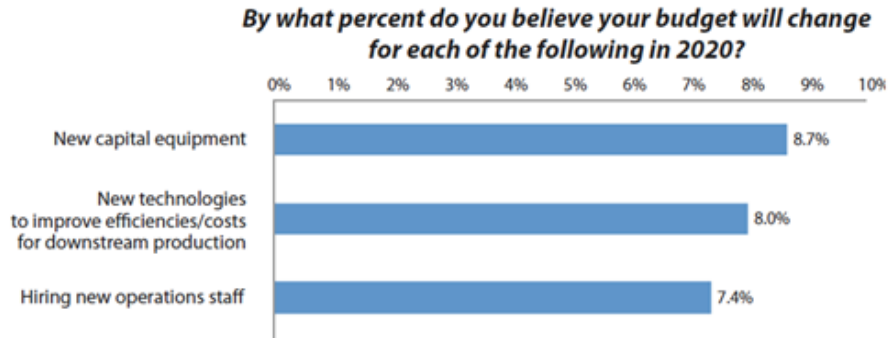
A Healthy Biopharma Industry

The biopharmaceutical industry and its associated suppliers, both equipment and services, continue to report rather consistent average 12% annual growth in terms of revenue (and most every other top-level indicator) over the past 25+ years. Worldwide sales of biopharmaceuticals (therapeutics) are now over $300 billion. Overall year-to-year industry revenue growth has been rather steady, with new product launches and increased sales of established products, including as products are approved for additional indications. New and innovative biopharmaceutical product types continue the trend of increasing the number and diversity of types or classes of biopharmaceuticals. This includes new(er) technologies or product types including cellular and gene therapies, antibody-drug conjugates (ADCs), live microbes as therapeutics, RNAi, etc.

With a very healthy pipeline of innovative and follow-on products, growth in international sales and expansions of R&D and manufacturing in response to the Covid-19 pandemic, industry revenue and activities can be expected to further steadily increase and drive further growth in biopharmaceutical R&D and manufacturing. The number of biopharmaceuticals in the development pipeline is now approaching 5,000. Must of this is attributable to mainstream large international pharmaceutical companies, which have by far the largest R&D and marketing capabilities. These companies now have biopharmaceuticals as >40% of their development pipeline.

This year, respondents continue to report growing bioprocessing budgets in essentially all 20 areas surveyed.

Fig 6: Selected Areas-- Average Change in Biomanufacturers' Budgets (2020)



Budgets for new capital investments in bioprocessing equipment continued to be an area for growth, cited by the largest portion, 8.7%, along with an 8% increase in budget for new technologies for downstream processing. And in response to another question, on average, budgets for outsourcing at individual facilities were reported increase by 14.5% in 2020.

Annual sales/revenue for bioprocessing supplies is a good indicator of the state and intensity of biopharmaceutical manufacturing (bioprocessing). Equipment, instrumentation, materials and suppliers are key parts of the industry. The average annual sales growth rate as reported by vendor survey respondents from 2007-2020 show the recent year's growth rate, 12.8%; a healthy growth rate, which most other industries would envy.

7 TREND:

High Product Costs and Threat of Price Controls

High costs of biopharmaceutical products, and related government-imposed price controls continue to be a threat to the industry. Product costs at the patient level are often considered exorbitant. As a result, potential price controls are particularly important in the U.S., by far the largest single source and market for biopharmaceuticals. Substantive changes in how U.S. developers set prices, and changes in U.S. government-imposed price controls will likely have global implications.

Major threats include political imposition of price controls, whether nationally by Congress or by individual States. Products could also not be sufficiently covered by insurers due to high costs, with patients essentially forced to use cheaper alternatives or even forego treatment. In an increasingly common example, a new cellular/gene therapy costing >$1 million for a course of treatment, even if 90% were covered by insurance, even a 10% 'co-pay' could be too expensive for most patients. Calls for more industry price regulation are ongoing in the U.S. where politicians from both leading political parties are proposing diverse price controls on pharmaceuticals. Alternatives that have been proposed include outcomes-based pricing for expensive products being based on patient response, such as payments only made if or for as long the treatment is successful.

Globally, there is a trend for imposition of pharmaceutical price controls by governments. This includes one of the largest and rapidly growing markets, mainland China, now the 3rd largest pharmaceutical market (after US and EU), increasingly imposing lower prices on (bio)pharmaceuticals as a condition for government health insurance coverage for the products. Many countries, both developed and developing, worldwide are increasingly promoting, or requiring use of lower cost biosimilar or biogeneric versions of mainstream biopharmaceutical products. The use of restrictive formularies by insurers, common in the U.S. and increasing in the various countries worldwide where health insurance is increasingly being adopted, with insurers essentially imposing price controls and restricting use of products they consider insufficiently cost-effective.

As industry trade associations 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 likely have adverse effects including inhibiting investment in product R&D, clinical trials, manufacturing and marketing. Price controls are portrayed as likely to reduce innovation.

Both biopharmaceutical and drug developers continue to generally follow the pattern of setting prices in major markets by making sure they charge lower prices in the sense that projected total healthcare costs are lower or more cost-effective vs. the current or prior treatment options/alternatives.

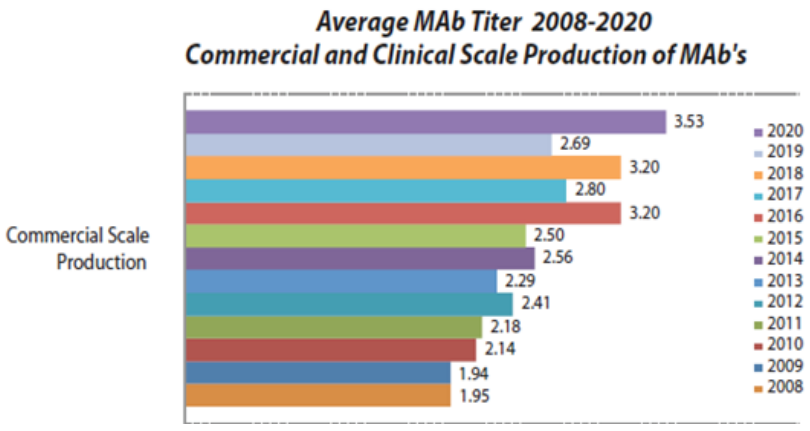
Costs of manufacturing continue to remain just a small portion relative to sales prices/revenue. So bioprocessing costs are generally not the primary cause of high product prices. For example, a typical monoclonal antibody product generally is estimated to have total costs for manufacturing in the 4-8% range of sales prices/revenue, while most cellular and gene therapies generally have manufacturing costs about 2x higher, generally in the >10% range.

8 TREND:

Productivity, Titers, Continue to Increase

Annual survey data and other sources confirm that bioprocessing productivity, particularly in terms of upstream titers and downstream yields (but to a much lesser extent) continue to incrementally increase. The Figure below shows year-to-year changes in survey respondents reporting the average mAb titers at larger scales at their facility. Keep in mind that titers back in the later 1980s-early 1990s were still usually only in the few 100s of milligrams (mg)/L, less than 10% of current average titers.

Fig 6: Average Titers for mAbs at Commercial Scales, 2008-2020



Related survey findings this year include:

- The average titer for reported new commercial-scale monoclonal antibody (mAb) upstream bioprocessing this year is 3.53 g/L, as shown above.
- The average titer for reported new clinical-scale mAb upstream bioprocessing this year is 3.96 g/L. (Commercial scale production generally older, dominated by older facilities and bioprocesses; clinical manufacturing is typically newer, with process innovations generally adopted at clinical scale). So average clinical scale titers are expected to be higher than those at older commercial scale processes.
- Overall, there is a clear trend for incremental increases in bioprocessing titers, the annual growth or CAGR for average titers from 2008-2020 at commercial scales is currently 5.1%, while the CAGR at clinical scales is 6.0%.

- In response to asking what "Factors will have the greatest impact on REDUCING YOUR COST OF GOODS for biotherapeutic products," the largest portion, 56.5%, cited "Improving production titer."
- Results from prior studies by BioPlan confirm a consistent incremental increases in titer over the past 3+ decades.1,2 These include a study of current and historical titer and yield data for many commercially manufactured products.

9 TREND:

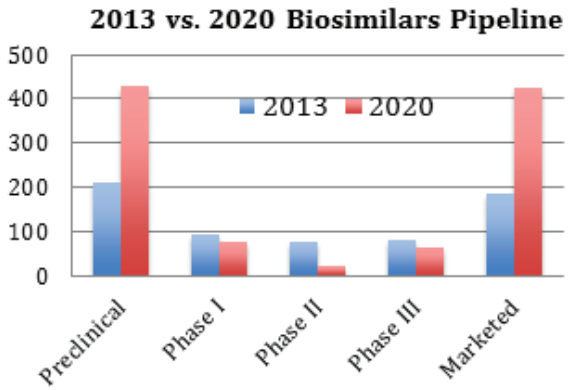
Biosimilars/Biogenerics - More Products & Players

The many follow-on products – biosimilars, biogenerics and biobetters - in development and entering world markets confirm 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 Directory (www.biosimilarspipeline.com; marketed by BioPlan) now reports 1,099 biosimilars (including biogenerics) in development or marketed worldwide, with 588 now in clinical trials or marketed in 1 or more countries. There are also >560 biobetters in development or marketed worldwide, with 296 in clinical trials or marketed. Over 800 companies worldwide are involved in follow-on products (biosimilar, biobetters and biogenerics), including many new entrants in both developed and developing regions. CMOs in recent years have reported about 15% increase in business attributed to biosimilars projects.

The status of biosimilars (here including biogenerics) in the pipeline in 2013 and mid-2020 is shown is the following Figure.

Fig 7: Biosimilars Pipeline by Phases of Development, 2013 and 2020



The number of products in the pipeline has significantly increased, particularly those in preclinical stage and marketed. The number of biosimilars in clinical trials has actually decreased, with much of this due to biosimilars now moving through clinical trials much

quicker once they enter trials, and with biosimilar approvals no longer being novel and being granted quicker than in earlier years. There are >419 biosimilar/biogenerics currently marketed (somewhere), with 83% (349) of these being 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 genuine biosimilar approvals). Most biogenerics are marketed in lesser-and non-regulated international commerce. There are ~80 biosimilars approved as genuine biosimilars (or equivalent) in major markets, primarily the U.S. and Western Europe.

Biosimilars (and biogenerics in lesser- and non-regulated international markets) are resulting in many new players entering the biopharmaceutical industry, and new manufacturing facilities being constructed. The largest number of biosimilars developers remain in the U.S. But Europe, India and China are the other major centers numerically for biosimilars.

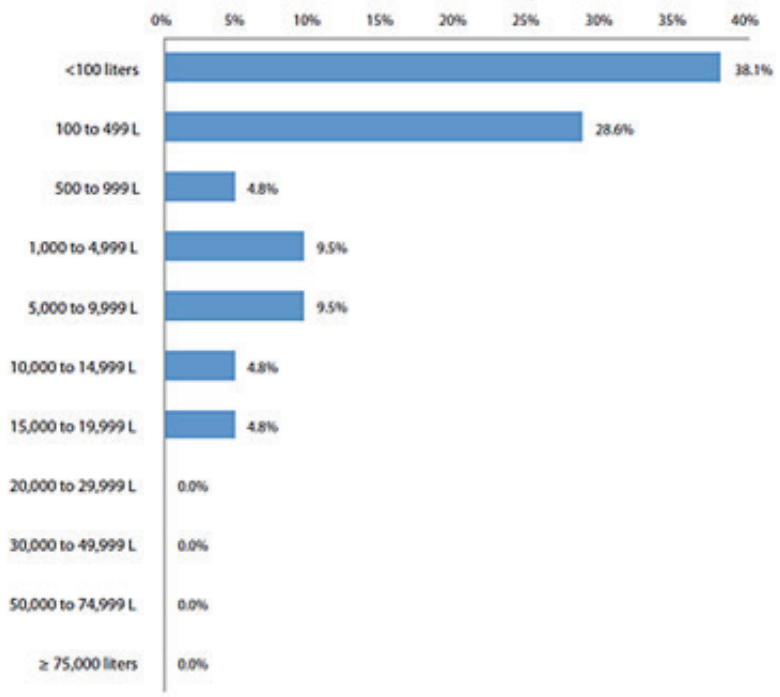
Biosimilars are also affecting the bioprocessing industry and its suppliers' markets. This includes nearly all biosimilar developers generally using single-use systems as much as possible. Competition will force developers to adopt optimally efficient and flexible bioprocessing technologies and facilities. Biosimilar manufacturers, many starting with no biopharmaceutical expertise or infrastructure, are often more receptive to adopting new technologies.[5-7]

10 TREND:

Cellular and Gene Therapies "Capacity Crunch"

This year's 17th Annual Survey included new questions related to cellular and gene therapies. The distribution of capacity among respondents reporting their facilities perform cellular/gene therapy bioprocessing is shown below.

Fig 8: Current Production Capacity Distribution, Cell or Gene Therapy



Most cellular and gene therapy facility manufacturing capacity remains skewed towards lower volumes. Among those involved in cellular or gene therapies, 2/3rds (66.7%) report less than 500 L total onsite bioreactor capacity. Gene therapy facilities generally have more capacity than cellular therapy facilities. Most cellular therapy facilities are still working with fully individualized one-off products, while viral vector manufacture for gene therapies is generally performed at larger scales and serving more patients per process run/batch, and has even been scaled up by some facilities to use of 2,000 L bioreactors.

BioPlan has published data concerning current and future cellular/gene therapies manufacturing capacity needs, including projecting a current and worsening "capacity crunch". We estimate that the current capacity shortfall in the cellular/gene therapy areas is 5x or 500%. That is, 5x current capacity would be in use, if it were available, particularly if this were hirable CMO capacity. This shortfall will increase.

Despite many new cellular and gene therapy facilities and expansions coming online and planned, there will be future shortages. Most every player, including leading CMOs, is still just working on expanding early and mid-phase clinical manufacturing, with few yet having scaled-up and establishing commercial/GMP manufacturing capacity. The very much needed ramping-up of cellular and gene therapy capacity is taking place in major market countries in parallel with Covid-19 pandemic and biosimilar products also ramping-up production capacity, with these trends potentially combining and worsening shortages of single-use and other shortages and experienced staff.

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, capacity and/or facilities among CMOs, or access due to long average wait times to get new projects started.

11 TREND:

Bioprocessing capacity continues to grow

BioPlan's Top 1000 Global Biopharmaceuticals Facilities Index (subscription database at www.Top1000Bio.com) reports and ranks the 1,625 biopharmaceutical manufacturing (bioprocessing) facilities worldwide in terms of known or estimated cumulative bioreactor capacity, onsite employment, number of products manufactured commercially and other facility and bioprocessing-related data. The source database now tracks 16.6 million L of production capacity worldwide, including all major facilities for the manufacture of recombinant and non-recombinant biopharmaceuticals, vaccines, and blood/plasma-derived products. About ≥70% or ≥ 11.6 million L is estimated to be mammalian-based, primarily for commercial manufacturing of monoclonal antibodies, and ≤ 30% or ≤ 5.0 million L is estimated to be microbial or other non- mammalian capacity (e.g., plant and insect expression systems). A regional breakdown of worldwide bioprocessing capacity is presented in Table 1.

Table 1: Regional Distribution of Total Worldwide and Regional CMO Capacities

Regioin	Regional Capacity, L	Facilities (no.)	Average Capacity/ Facility, L	Capacity (CMOs), L	CMO Facilities (no.)	Average CMO Capacity
US/N. Amer.	5,500,000	583	9,400 L	1,150,000	201	5,700 L
Europe	6,000,000	457	12,300 L	1,250,000	186	6,700 L
Asia/ROW	4,700,000	539	6,700 L	1,400,000	142	9,800 L
Total WW	16,600,000	~1,600	9,700 L	3,500,000	542	6,800 L

The U.S., with its greater emphasis on innovation, R&D, process development and clinical manufacturing, numerically has the most bioprocessing facilities, while Europe has greater bioprocessing capacity, with European facilities larger on average. Asian facilities are approaching the U.S. in terms of numbers, while their average capacity remains lower. In terms of CMOs, Asia/ROW has the most capacity, but this is much more highly concentrated, including a few super-sized facilities such as those of Celltrion and Samsung in S. Korea. The U.S. has the largest number of CMOs, including a good number of new cellular/gene therapy CMOs coming online; and much as with overall capacity, the U.S. CMO facilities are on average lower than the other regions.

Over 880 facilities worldwide now each have ≥1,000 L estimated bioprocessing capacity; over 1,110 facilities have ≥500 L capacity. 'CMOs' now include some very large commercial manufacturing facilities, mostly in the U.S., offering contract bioprocessing services, with these tending to inflate the reported total capacity assigned to CMO tasks.

The majority of bioprocessing capacity worldwide continues to be held by a relatively small number of the largest facilities. For example, the total >6.5 million L reported for just the top 10 leading facilities comprises ~40.0% of the total estimated worldwide capacity. The 100 largest facilities have around two-thirds of worldwide capacity. It must be kept in mind that the majority of the massive capacity held by the top leaders involves legacy ≥ 10,000 L bioreactor-anchored stainless-steel facilities. Relatively few such facilities are now being constructed in the U.S. and W. Europe, with manufacturing in major market countries increasingly using single-use systems.

12 TREND:

FDA and New Product Approvals

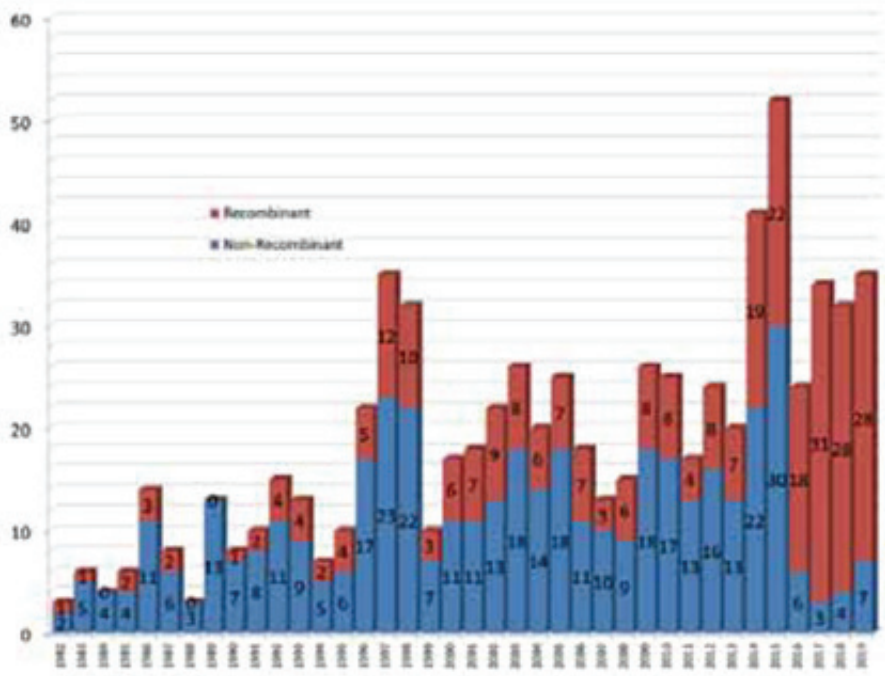
FDA (and nearly all other major market regulatory agencies) has matured along with the biopharmaceutical industry, and in many respects the agency remains the industry's primary gatekeeper, determining who and what gets to enter the largest (the U.S.) market. FDA biopharmaceutical approvals have been steadily increasing. Now, over 10 years after implementation of biosimilars approvals, these and mainstream biologics approvals and related FDA actions are in general running smoothly, including becoming more predictable.

The agency has adopted major changes in many areas and is well prepared to deal with near-term challenges. This includes FDA largely already adapting to handling many new product classes and technologies, such that there few biopharmaceutical-related areas or issues that it hasn't yet dealt with. This includes the agency adapting to biosimilars, orphan and super-orphan products, antibody fragments, antibody-drug conjugates (ADCs), cellular therapies, viral vector gene therapies, individualized therapeutics, therapeutics dependent on diagnostics outcomes, biologics NDAs being converted to BLAs, various types of accelerated approvals, more use of biomarkers vs. clinical data, and other recent changes and advances. FDA and other regulators appear to also have adapted, at least in terms of performing the most basic functions including product approvals, to the near-term impacts of the Covid-19 pandemic.

The agency has demonstrated a solid track record in new and challenging product and technology areas. Changes in regulations and FDA activities in coming years can be expected to be associated with pandemic and biodefense products and issues, with pandemic responses perhaps causing major changes in approvals comparable to those major implemented in response to the HIV/AIDS epidemic. For example, many expect efforts by FDA to further speed-up evaluations of approval applications.

The Figure below presents the number of biopharmaceutical products approved by FDA (BLAs/NDAs) from 1982, the year of the first recombinant product (insulin) approval through 2019 using our definition of biopharmaceutical as being biotechnology (live organism)-manufactured pharmaceuticals.

Fig 9: FDA Approvals of New Biopharmaceutical Products 1982-2019



In the most recent full year, 2019, FDA approved 35 biopharmaceuticals. The great majority, 28 (80%), have recombinantly manufactured active agents. Recombinant monoclonal antibodies (mAbs), including derived fragments, were the product class with the most approvals, 15 (43%). Seven (20%) non-mAb recombinant proteins received approval. One gene therapy and zero cellular therapies received approval.

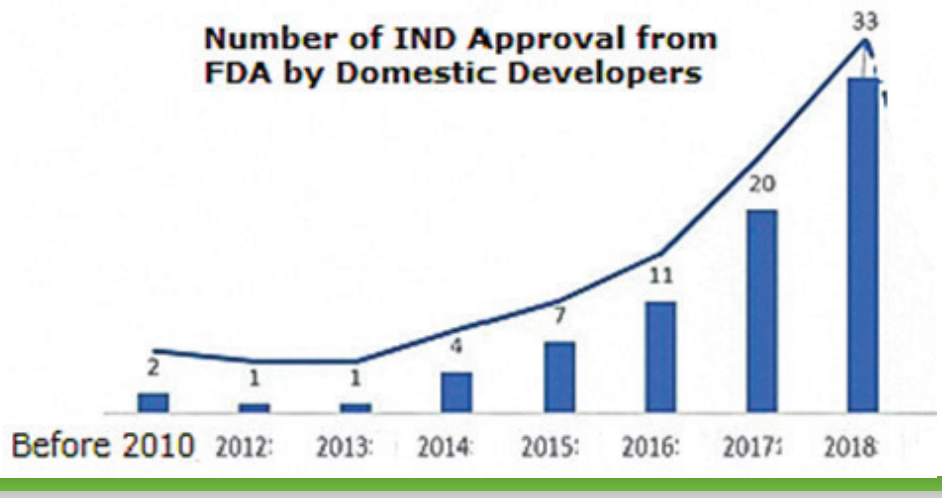
Ten biosimilars received approval. A total of 22 (63%) follow-on-type products, either biosimilars or equivalent 505(b)(2) generic drug approvals (for biologics), received approval. In terms of companies, the majority of approvals (18; 51%) involved companies receiving multiple relevant approvals in 2019. The great majority (29; 83%) of approvals went to Big (Bio)Pharma companies, a record number and also a record percentage in all but the earliest years examined.

13 TREND:

China CMOs – A Major New Biopharma Participant

BioPlan recently published an extensive study and directory of CMOs in China (PRC) (Growth of CMOs in China, June 2020). China is experiencing rapid growth of its domestic biopharmaceutical industry and its bioprocessing activities. This includes production to meet growing demand from the huge domestic population, particularly expansion of the manufacture of biogeneric monoclonal antibodies for domestic consumption, with this increasing in parallel with growth in innovative biopharmaceutical R&D and manufacturing and rapid expansion of CMO capacity in China. The increase in IND applications filed by China-based developers to conduct clinical trials in the U.S. (and presumably Europe and other major markets) is increasing at an accelerating rate, as shown in the following figure. The products involved are likely mostly innovative products, while some will be seeking formal biosimilar approvals.

Fig 10: IND Applications to the U.S. from China



CMOs are how most foreign (non-Chinese) developer companies and bioprocessing professionals will encounter and perhaps do business in China; and use of CMOs by biopharmaceutical developers in China is increasing. The number and size of China-based CMOs, including those serving domestic and international customers, in China are expanding for key reasons including.

- **There are more biosimilars** (called this in China, but more accurately 'biogenerics') and innovative biopharmaceuticals entering the clinical pipeline and moving towards commercial manufacturing.

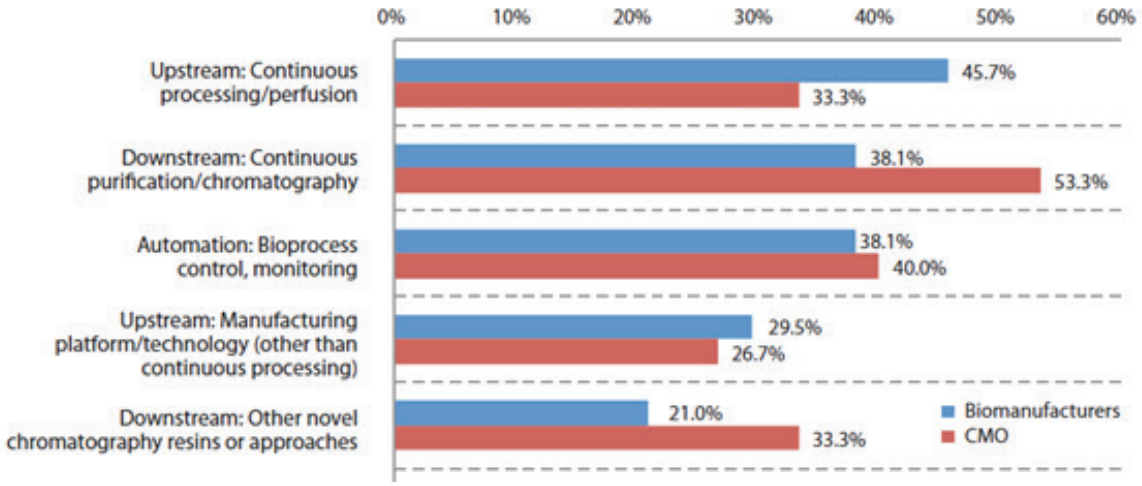
- **Biologics development and their commercial scale manufacturing is relatively new in China –** the country is just getting started. Most product developers in China lack bioprocessing capacity, including early-stage manufacturing facilities, and/or their staff lack needed bioprocessing and regulatory knowledge and expertise, so use of CMOs is a necessity.
- **A growing number of domestic biopharmaceutical developers,** most concerned with biogenerics/biosimilars, with a small but rapidly growing number pursuing innovative product development. As BioPlan's top Chinese bioprocessing facilities directory shows, there are now over 100 companies in China developing Mabs (http://bioplanassociates.com/china-top-60/).
- **Bioprocessing capacity is growing in China.** BioPlan's Top 1000 Global Biopharmaceutical Facilities Index (free version at www.top1000bio.com) now reports China having a total of >1.5 million L bioprocessing capacity, about 9.2% of worldwide capacity, now surpassing India (at .98 million L) by over 50%.
- **Central government laws/regulations** that ruled out biopharmaceuticals being manufactured by CMOs or other 3rd parties are now changing.
- **The Chinese domestic population** and potential biopharmaceutical market are the largest of any country. Just addressing domestic needs, including as China prosperity grows and health insurance starts to be more common, will require rapid growth of domestic bioprocessing capacity.
- **Interest and expectations among Western companies for outsourcing bioprocessing to China are increasing.** In response to asking U.S.-based survey respondents, China was cited by 40.0% as an outsourcing destination (compared with only 2.8% in 2009).

14 TREND:

Continuous Bioprocessing on Track

This year when asked what bioprocessing innovations are most needed, respondents continued to very frequently cite aspects of continuous bioprocessing. "Upstream Continuous processing/perfusion" was cited by a total of 44.2%, and "Downstream: Continuous purification/chromatography" systems was cited by 40.0% as expected to evaluated/tested by their facility within the next year (with respondents able to specify multiple answers). It can be readily assumed that a majority of bioprocessing facilities expect to evaluate at least some part of continuous processing this year.

Fig 11: Novel Bioprocessing Systems/Innovations to Evaluate in Next 12 Months (Biomanufacturers vs. CMOs)



Continuous bioprocessing clearly was the primary area where evaluation/testing is expected within a year, with upstream and downstream continuous processing reported as the number 1 and 2 most common responses. Note that the CMOs (vs. developers/biomanufacturers) cite downstream continuous bioprocessing at much higher rates, with developers citing upstream continuous processing (perfusion) more than CMO respondents. The largest difference in expectations for testing this new technologies between developers and CMOs was with "Downstream: Continuous purification/chromatography systems," with 53.3% of CMO respondents but only 38.1% of

developers expecting to evaluate products/technologies in this area in the next 12 months. However, there is yet no major rush to adopt continuous processing. Overall, implementation of continuous bioprocessing remains low. At best a few of the many specific unit process/steps both up- and/or downstream have been implemented as continuous by a minority of facilities. A select few manufacturers have long been using upstream perfusion for commercial manufacturing, mostly for products that require perfusion's generally milder/less intense processing conditions, including Factor VIII and related coagulation factors, with these having been manufactured since their very start, for decades now, using perfusion (and with a few products also using continuous centrifugation). BioPlan studies have shown only ≥5% of bioreactors over desktop size use perfusion, with most current use with feeder, not production, bioreactors. There is much more adoption of perfusion for small-midscale vs. large/commercial scale manufacturing.

BioPlan studies have shown that few processes are being scaled-up using perfusion/continuous upstream processing, particularly scale-up for commercial GMP manufacturing. Looking downstream, continuous chromatography technologies, such as simulated moving bed (SMB) and periodic countercurrent chromatography, are generally not yet considered ready for commercial-scale manufacturing adoption.

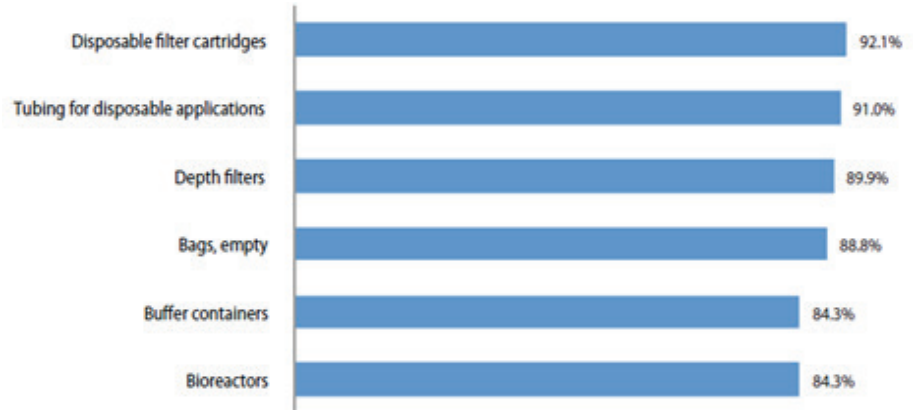
15 TREND:

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. Single-use systems adoption will increase as the growing number of new products now being developed using single-use systems move through the pipeline to clinical scale manufacturing and on to cGMP commercial production using single-use systems.

Again, this year for the two-dozen SUS areas surveyed, well over 80% of survey respondents reported considerable current use of single-use bioprocessing equipment. The reported percent of applications at all stages of R&D and manufacturing significantly using leading classes of single-use equipment is shown below, with only those cited by >75% of respondents included.

Fig 12: Selected Areas: Usage of Disposables in Biopharmaceutical Manufacturing, Any Stage of R&D or Manufacture, 2020



Note that 84.3.% report use of single-use bioreactors, with use of these generally indicating much wider use of single-use equipment as part of the same processing lines. 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”, and “Perfusion devices” adoption.

There is a clear trend for new(er) facilities and expansions being designed to single-use vs. stainless steel-based bioprocessing. Costs of non-blockbuster scale product commercial manufacturing using single-use system are now considered competitive with stainless steel systems, with many claiming single-use is overall cheaper. This trend for even more single-use includes more products being developed that will use single-use bioreactors and process lines for commercial manufacture, generally anchored by one or scaling-out with multiple 2,000 L single-use bioreactors.

It is now widely recognized that single-use system-based bioprocessing can reduce facility costs, size, and provide faster changeovers and reduced times in bioprocessing. Industry ramping-up manufacture of Covid-19 and other pandemic products include expectations for more adoption of single-use systems for commercial manufacturing.

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