BPSA 2020 Speaker Series

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10:30-11:15 AM EDT

Trends in Bioprocessing that Affect Single-Use Technologies and Adoption

Featured Speaker
Eric Langer,
BioPlan Associates

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TOP 15 TRENDS IN BIOPHARMACEUTICAL MANUFACTURING, 2020

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Current Major Trends Affecting Biopharmaceutical Manufacturing:

Underlying Trends-Driving Others

- Expanding: **12% Growth** - biopharmaceutical sales
- Worldwide **>$300 billion/year**
- Biopharm now nearing **50% of Therapeutic Pipeline** / R&D
- Pandemic has rekindled **excitement & promise** of biologics

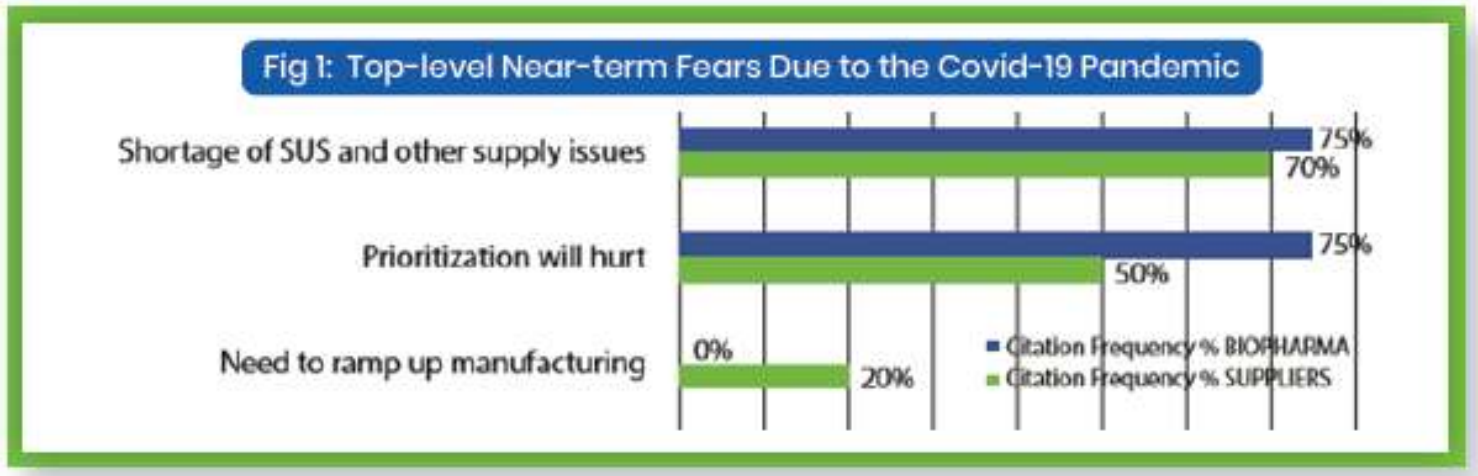
Optimistic future for bioprocessing; more:

- Biologics, with smaller markets, more orphan and personalized products
- Bioprocessing facilities worldwide, especially in major markets and Asia
- Cellular and gene therapies facilities, commercial manufacturing
- Single-use systems at clinical scale;
- SUS for commercial scale; multiple 1,000-2,000 bioreactors; fewer new commercial scale stainless steel facilities
- Modular-constructed facilities and cleanrooms
- Flexible manufacturing facilities, manufacture of multiple products
- Cloning major market GMP facilities in developing countries
- Biosimilars, biobetters and biogenerics, capturing growing market shares
- Continuous processing: upstream perfusion, DSP continuous chromatography @ commercial scale, coming years
- Efficiency and productivity in bioprocessing as titers and yields continue to incrementally increase
- Process automation, monitoring, control and data recording/processing, PAT, etc., built into bioprocessing equipment
- Modeling, data mining, PAT, QbD; down-scale modeling, mini- or even micro-bioreactors increasingly important
- Improved expression systems, CRISPR and other genetic engineering advances

2020 17th Annual Report

- 150 Biopharmas, CMOs
- 130 Industry Suppliers
- 23 Countries
- *www.bioplanassociates.com/17th*

1 TREND: Biopharma Industry has quickly adapted to the Covid-19 pandemic



Key Fears and Resolutions

- ***"Shortage of SUS & other supplies"*** inability to obtain needed SUS
- ***"Prioritization will hurt."*** [non-Covid-19 projects] as they prioritize activities, pushing pandemic/ biodefense-related to the front of the line.
- ***Real Shortages:*** Prioritization combined with worsening of ongoing SUS shortages (causing order lead/wait times) resulting in problems w/equipment and CMO services
- ***Developers have more 'fears'*** regarding shortages and prioritization vs. suppliers.

Near-term Covid-19 Responses (short term trends)

- Biopharma R&D and bioprocessing facilities worldwide are now considered 'essential' by most countries.
- Nearly all bioprocessing facilities continuing work throughout pandemic without significant interruption.
- Most facilities expect to increase R&D and bioprocessing, often due to displacement of non-pandemic projects at other facilities.
- Personnel changes: Facilities isolating groups of workers; shifts; only a few at a time in labs or mfg suites
- R&D and bioprocessing, other staff working from home, as possible.
- ***Strategic attention to robustness and security of supply chains and inventory; holding 12-18 months' vs 6-12 months of supplies.***

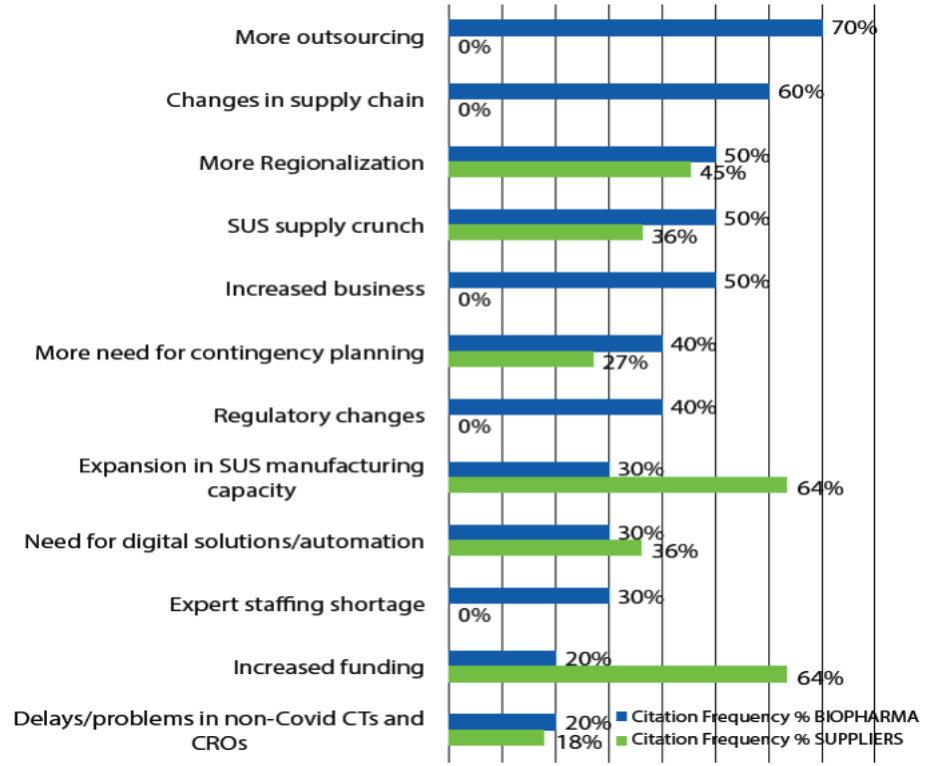
2 TREND: Longer-term Responses to Pandemic Will Bring Many Changes

Major changes to biopharma industry yet to come, as industry responds to the pandemic.

10s of $billions in funding for pandemic- and biodefense-related vaccines /therapeutics /R&D and manufacturing. Billions of doses to be produced Annually.
…In addition to pre-pandemic product manufacturing.

Sector has adapted to the ongoing Covid-1 pandemic; Long-term, the industry will resolve the Covid-19 pandemic, and **will position itself to more effectively address potential for *future pandemics*.**

Fig 1: Long-term Effects of Covid-19 on Bioprocessing



Biopharma executives: Top long-term effects:

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

3 TREND: Manufacturing Productivity Still Most Important Trend

Trend driven by need for more productivity, quality, and cost reductions in manufacturing processes. To remain competitive, the industry continues seek to:

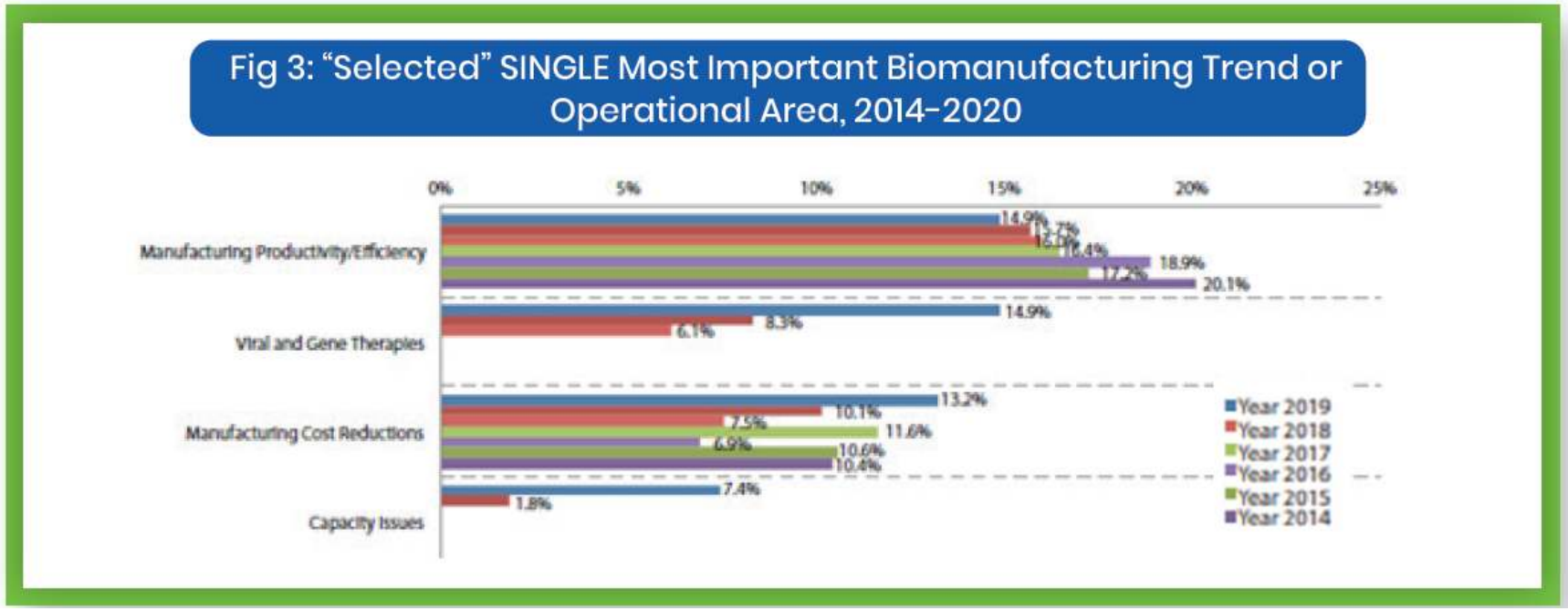
a) Decrease time-to-market (speed-to-market).

b) Decrease manufacturing costs / complexity

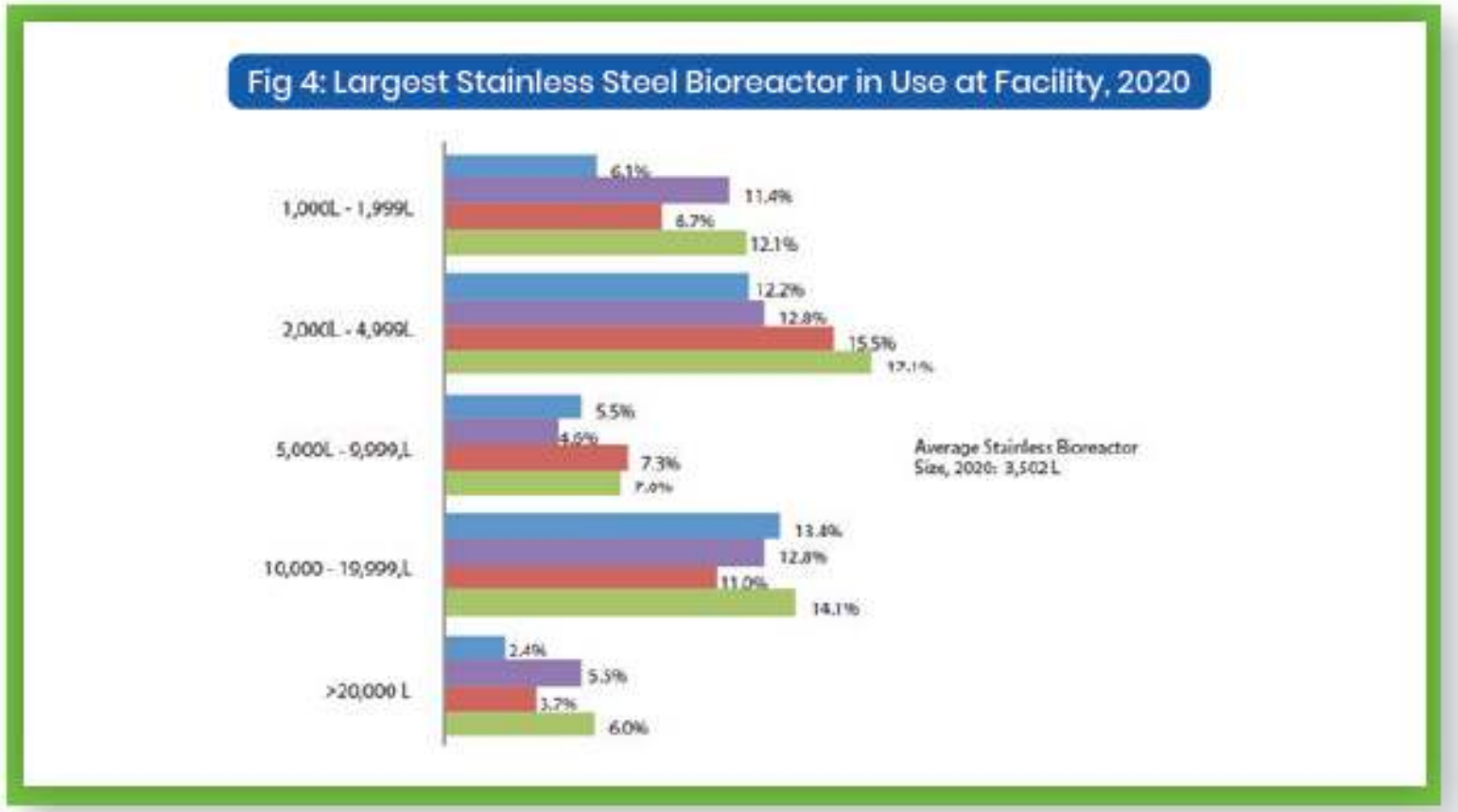
c) Intensify processing, increase titers / yields smaller footprints, etc.

d) Streamline new tech, equipment testing to make adopting new technologies quicker.

e) Increase clinical and commercial manufacturing output



5 TREND: Stainless Steel Bioreactors: Smaller Installations

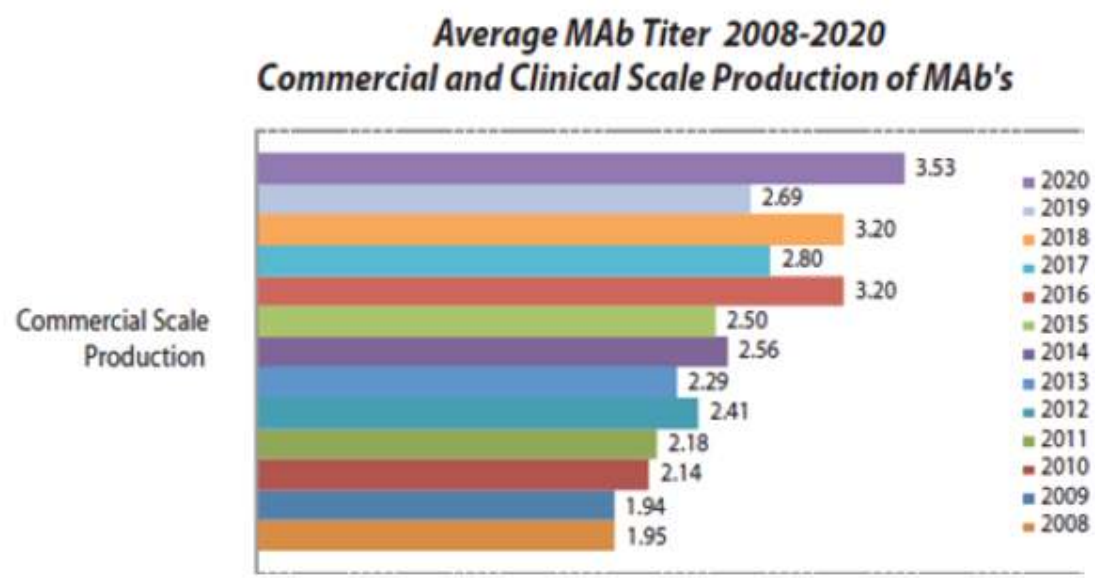


Fewer new stainless bioreactors installed; more SUS facilities coming online

- Continued reduction in volume of steel bioreactors (smaller)
- Average stainless-steel capacity was 3,502 L (3,694 L in 2018).
- Nearly every ‘largest’ onsite steel bioreactor size range has shown an overall decrease in recent years.
- Facilities w/ largest stainless bioreactor ≤1,000 L has been increasing (now 38%)
- Fewer facilities reporting large bioreactors ≥2,000 L, (2K generally a current cut-off for SUS bioreactors).

8 TREND: Productivity, Titers Increase

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



Average titer new commercial mAb bioprocessing = **3.53 g/L**

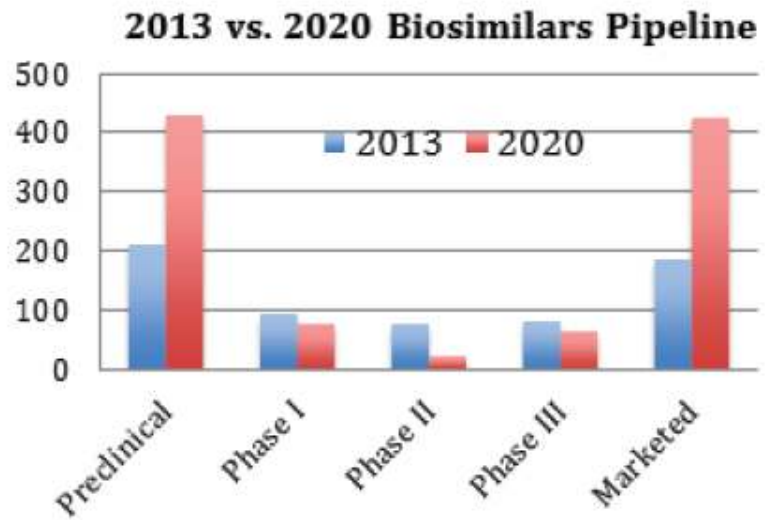
Avg titer new clinical-mAb bioprocessing = **3.96 g/L.**

Commercial scale generally older vs clinical (newer, innovative; average clinical titers expected to be higher)

Increases in titers 2008-2020
Commercial **5.1%, CAGR**
Clinical scales **6.0% CAGR**.

9 TREND: Biosimilars/Biogenerics - More Products & Players

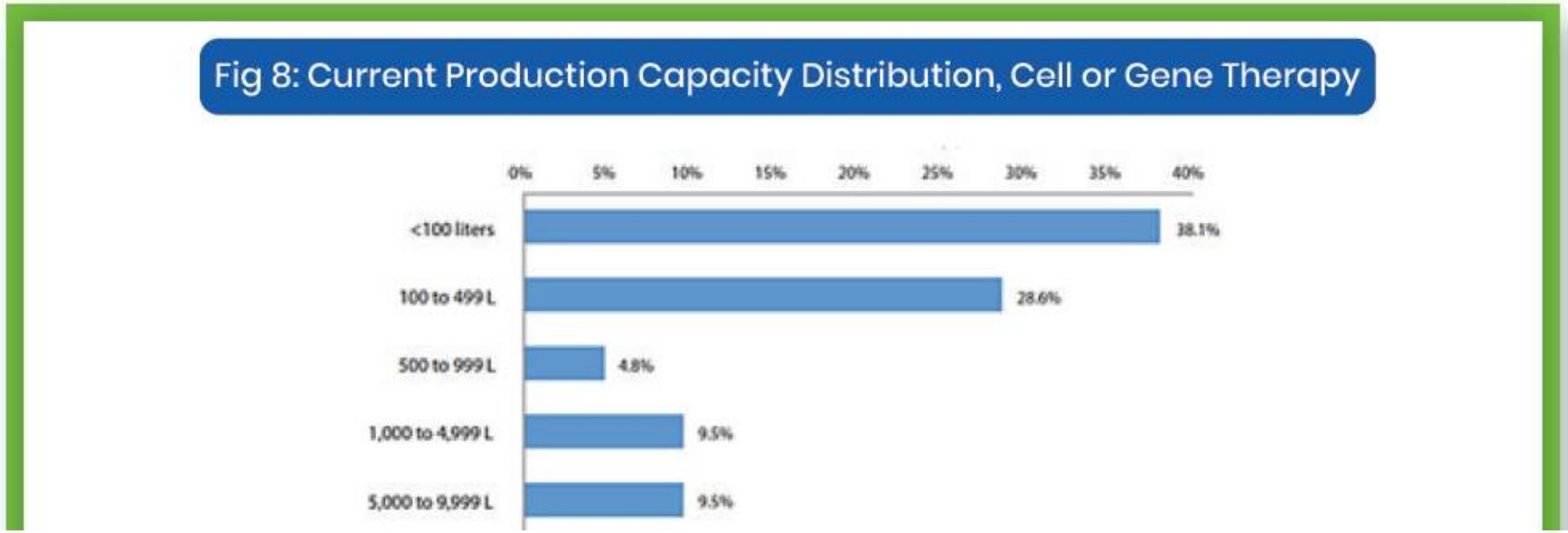
Fig 7: Biosimilars Pipeline by Phases of Development, 2013 and 2020



Biopharma industry is maturing; major blockbuster products going off-patent.
Biosimilars/Biobetters Pipeline Directory (*www.biosimilarspipeline.com*):

- **1,099** biosimilars and biogenerics, with **588** in clinical trials or marketed.
- **560** biobetters.
- Over **800** companies worldwide involved
- Many new entrants in developed and developing regions.
- CMOs report 15% increase in business attributed to biosimilars projects.

10 TREND: Cellular and Gene Therapies "Capacity Crunch"



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

Cellular and gene therapy facilities manufacture at lower volumes.

66.7% report less than 500 L bioreactor capacity.
GT facilities generally have more capacity than CT facilities.

Most CT facilities still work with individualized one-off products;

Viral vector manufacture for GT is performed at larger scales; scaled up by some facilities to use 2,000 L bioreactors.

11 TREND: Bioprocessing capacity growing

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

BioPlan's Top 1000 Global Biopharmaceuticals Facilities subscription database at www.Top1000Bio.com reports and ranks **1,625 biomanufacturing (bioprocessing) facilities worldwide** in terms of 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.
~70% or ≥ 11.6 million L is mammalian-based, primarily for commercial mAbs, ≤ 30% or ≤ 5.0 million L is microbial or other non-mammalian capacity (e.g., plant and insect expression systems).

- U.S. has the most bioprocessing facilities;
- EU has greater bioprocessing capacity, larger facilities.
- Asia approaching the U.S. in #s, at much lower capacity.
- CMOs in Asia/ROW have the most capacity, (a few super-sized facilities Celltrion and Samsung in S. Korea).
- U.S. has the largest number of CMOs, including new cellular/gene therapy CMOs coming online

Over 880 facilities worldwide now each have ≥1,000 L
Over 1,110 facilities have ≥500 L capacity.

Majority of bioprocessing capacity held by a small number of the largest facilities:
>6.5 million L reported for the top 10 facilities comprises ~40.0% of the total estimated worldwide capacity.

- The 100 largest facilities have around two-thirds of worldwide capacity.
- 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.

13 TREND: China CMOs – A Major New Biopharma Participant

Increase in IND applications filed to US FDA by China-based developers to conduct clinical trials in the U.S. increasing at an accelerating rate.

CMOs are how most non-Chinese developer companies will do business in China; CMO use is increasing. Number and size of China-based CMOs, including domestic and international customers is expanding.

BioPlan study of CMOs in China (PRC) (June 2020).

China is experiencing rapid growth of its domestic biopharmaceutical industry. Production to meet huge domestic needs, consumption.

Chinese domestic population largest of any country. Just addressing domestic needs, including as China prosperity grows and health insurance starts will require rapid growth of domestic bioprocessing capacity.

More biosimilars ('biogenerics') and innovative biopharmaceuticals entering the clinical pipeline and moving towards commercial manufacturing.

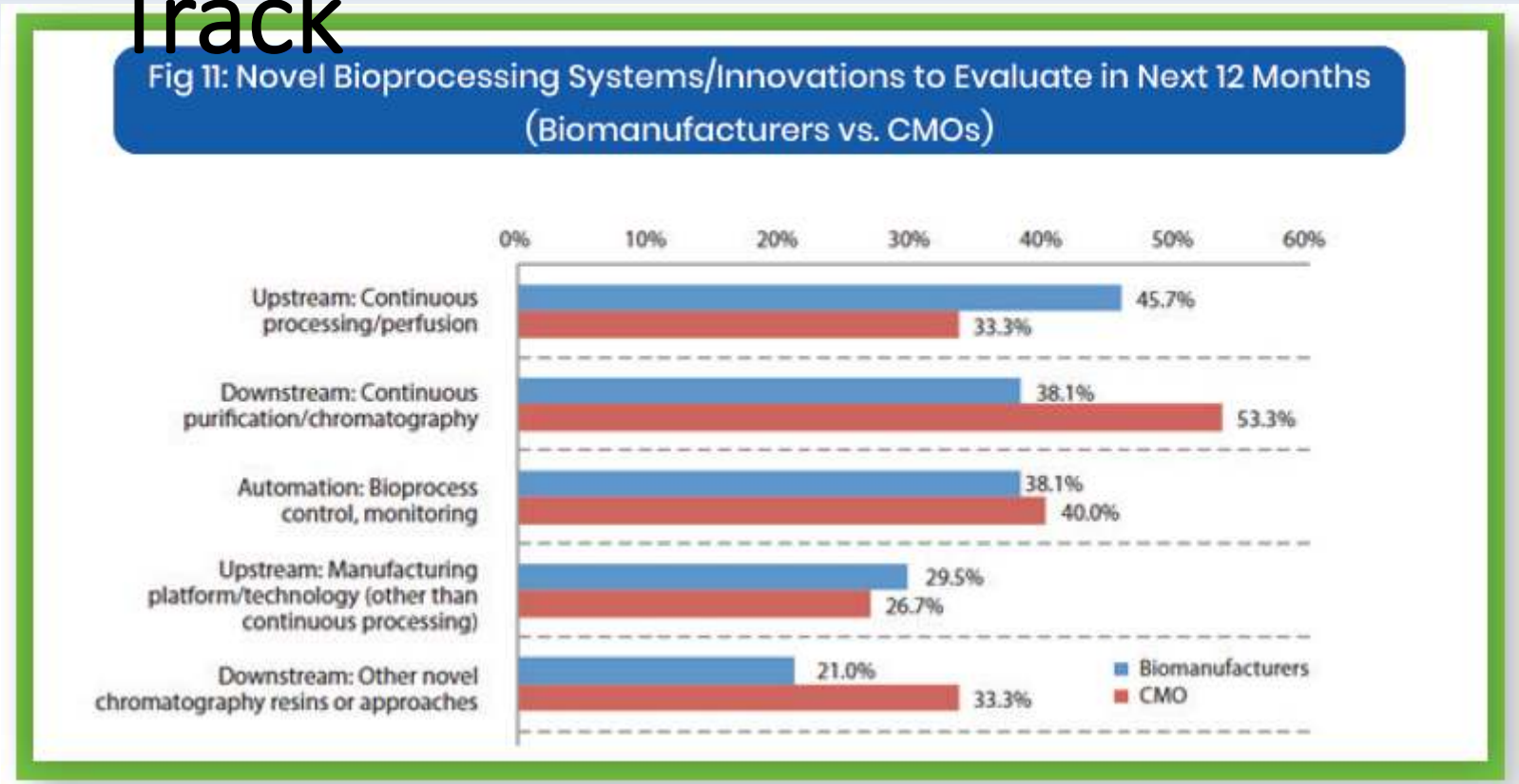
Biologics development and commercial manufacturing relatively new in China –Most developers in China lack bioprocessing capacity, staff lack bioprocessing / regulatory knowledge, expertise, **use of CMOs is a necessity.**

More domestic biopharmaceutical developers, most biogenerics/biosimilars, a small but rapidly growing innovative product developments. BioPlan's Chinese bioprocessing facilities directory shows over 100 companies in China developing Mabs (http://bioplanassociates.com/china-top-60/).

Bioprocessing capacity growing in China. BioPlan's Top 1000 Global Biopharmaceutical Facilities Index (subscription www.top1000bio.com) China has >1.5 million L capacity, about 9.2% of worldwide capacity, surpassing India by over 50%.

Interest among Western companies for outsourcing to China increasing. China cited by 40.0% as an outsourcing destination (vs only 2.8% in 2009).

14 TREND: Continuous Bioprocessing on Track



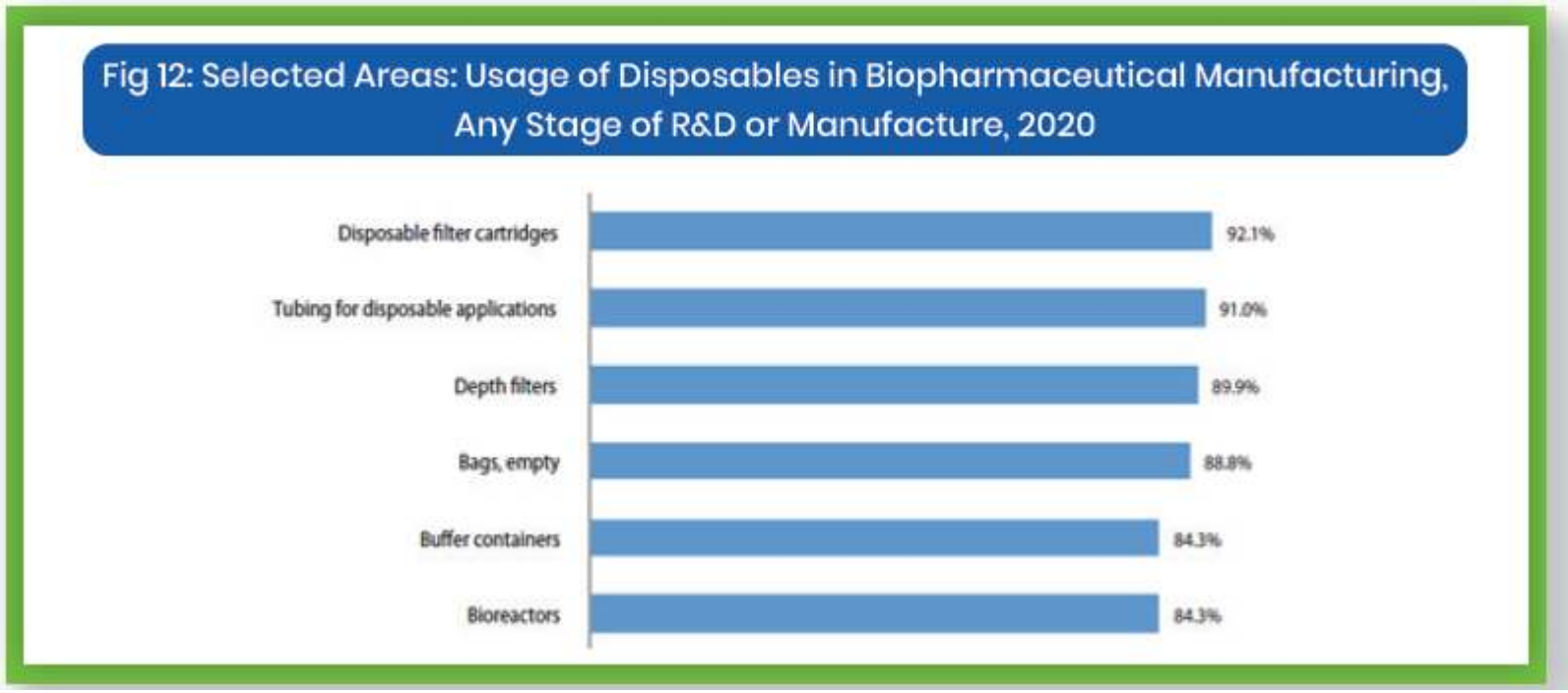
"Upstream Continuous processing/perfusion" to be evaluated in the next 12 months by 44.2%

"Downstream: Continuous purification/chromatography" systems cited by 40.0%

Possible that a majority of facilities will evaluate at least *some* continuous technology this year.

However, there is yet no major rush to adopt continuous processing. Overall, implementation of continuous bioprocessing remains low. Just a few of the many specific unit process/steps both up- and/or downstream have been implemented as continuous.

15 TREND: Single-use Still Growing



- BioPlan estimates ≥85% of pre-commercial (R&D & clinical) products now involve considerable SUS mfg.
- Adoption will increase as clinical scale products move on to cGMP commercial production using SUS.
- >80% of survey respondents reported considerable current use of single-use bioprocessing equipment.

84.3.% report use of single-use bioreactors, generally indicating much wider use of single-use equipment as part of the same processing lines.

Annual **(adoption) rates** in SUS usage…first usage within the facility (not revenue growth) was highest, **11.5%, for "Membrane adsorbers,"** followed by "**Mixing systems", and "Perfusion devices" adoption.**

Costs of non-blockbuster scale commercial manufacturing using SUS now considered competitive with stainless; many claiming single-use is overall cheaper.

Expect more SUS biologics will use single-use bioreactors at commercial scale, scaling-out with multiple 2,000 L SUS bioreactors.

Widely recognized: SUS-based bioprocessing reduces facility costs, size, faster changeovers reduced bioprocessing time.

Industry ramping-up manufacture of Covid-19 and other pandemic products: expect more SUS adoption for commercial manufacturing.

Questions

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