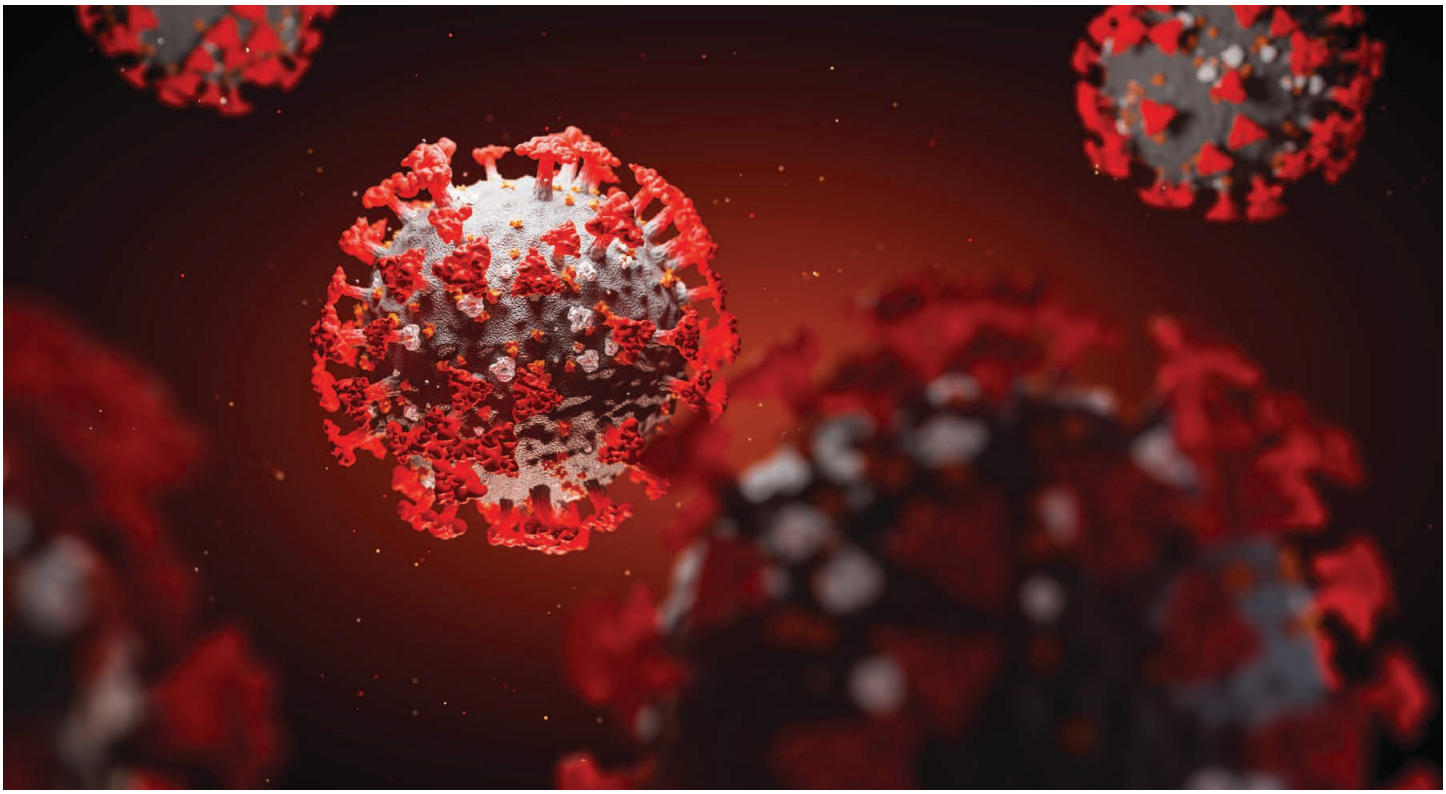
From meeting demand to the new normal: how biologics production is shifting in response to SARS-CoV-2

Following the emergence of the novel coronavirus SARS-CoV-2 in late 2019, strong social, economic, and environmental impacts have been felt globally. In fact, many countries will continue to face recession challenges well into 2021.

While SARS-CoV-2 infections have adversely impacted nearly all industries and social functions worldwide, the biopharmaceutical and bioprocessing industries are standing out as somewhat of an exception [1]. In May 2020—due to global restrictions—a small decline was projected for the biologics market, from US$269.2 to $239.2 billion, with a dip in the compound annual growth rate (CAGR) of –11.2%. Despite this slowdown, the biologics market is still expected to grow at a CAGR of 15% from 2021 and is projected to reach US$464.7 billion by 2023 [2]. Additionally, in August 2020, Technavio projected a CAGR of 13% for the global cell culture market from 2020 to 2024, with a 12% projected increase in 2020 compared to 2019 [3]. However, these projections can fluctuate due to the nature and daily changes of the crisis.

Regardless of the virus's impact on the biologics market, it is not "business as usual" for the global bioprocessing industry. Almost a year into this crisis, trends are beginning to emerge that will likely carry on for years to come.



The race for new therapies

From developing new vaccines and treatments, to repurposing drugs to help fight the virus, the global bioprocessing industry has been working hard to bring therapies quickly to market in order to meet demand without having to compromise on overall quality. On average, vaccine development takes 10 years, but with increasing demand to fulfill this critical need faster, developers are reducing this time frame to 12–18 months [4,5].

The pressure is on to manufacture and distribute a vaccine that will ultimately allow for a return to "normal life". SARS-CoV-2 vaccine candidates range from DNA and RNA platforms to recombinant proteins, live-attenuated viruses, and viral vectors. Each of these vaccine types has its own advantages and challenges when it comes to R&D, manufacturing, and eventual distribution and administration. "Classical" vaccine platforms, such as the measles vaccine, introduce a weakened (attenuated) or inactivated version of the virus into the body. Protein subunit vaccines require the identification and production of an antigen, while more modern vaccine platforms—such as viral vectors and nucleic acid based (mRNA or DNA) vaccines—actually use the patient's own body to manufacture the antigen. As of December 22, 2020, 61 vaccine candidates were in clinical evaluation [6]. Vaccines based on nonreplicating viral vectors, inactivated viruses, protein subunits, RNA, and virus-like particles make up the 13 candidates that have reached Phase 3 large-scale efficacy trials currently [6].

Recently, three vaccine candidates have shown initial successes, with data from their Phase 3 trials showing efficacy against SARS-CoV-2 [7-9]. In addition, two mRNA vaccine candidates have been shown to be 94.1% and 95% effective, respectively, with both candidates now authorized for use in a number of countries [8-12]. The number of vaccine candidates is regularly changing, with more progressing through clinical trials. However, with over 700 different vaccines, antiviral drugs, and other therapies in development, the bioprocessing materials supply chain has become threatened [13,14].

Shortages in bioprocessing solutions and consumables—for instance, cell culture media, feeds, supplements, single-use bags, vessels, and many more—are occurring as demand is far outweighing the supply [13]. This frenzy of biologics development associated with SARS-CoV-2 is likely to have a lasting impact on the bioprocessing materials supply chain [13].

Additional challenges associated with the development of specific types of vaccine therapies include storage requirements, the cold chain, and community administration and distribution [15]. Barriers related to storage requirements may impact stability and in turn affect delivery and distribution of approved vaccines [16]. For instance, some promising mRNA vaccines—both those authorized and in development—may run into supply issues as ultracold storage conditions are required for their stability. In contrast most protein subunit vaccines can be held at refrigerated temperatures for months [16]. Complex storage requirements that have the potential to limit access in emerging markets highlight the difficulty of developing a vaccine that works both safely and effectively across different populations and locations [5]. Generating sufficient vaccine data (i.e., demonstrating effectiveness and safety in different conditions) is also a challenge, especially when the timeline to market is shortened. Typically, it takes 5–10 years to generate a clinical package to potentially gain regulatory approval for a vaccine [5].

The industry is also searching for alternative and novel ways to repurpose capacity and technologies to support the response to the SARS-CoV-2 crisis. The sudden and unexpected need to develop new therapies has resulted in disruptive and chaotic demand for resources, personnel, and facility space. This may lead to challenges for biologics already established in the manufacturing pipeline.

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Keep calm and carry on

Planned forecasting, investment, and the inertia built into pharmaceutical pipelines make it difficult to shift manufacturing projects [1]. This implies minor changes and a low risk of major disruptions to the biologics industry in the short term—a benefit for patients who require treatments unrelated to SARS-CoV-2 infections [1]. Nonetheless, as a result of global shortages, social distancing measures, and prioritization of supplies, cascading effects are being observed and felt in the bioprocessing industry.

Prioritization of supplies and services for SARS-CoV-2–related bioprocessing is an ongoing challenge; suppliers are concerned that the uptick in vaccines and therapeutics is resulting in shortages of single-use technologies and other materials [1]. Orders and outsourcing requests for SARS-CoV-2–related supplies have been made a top priority and this will only continue as more of these vaccines and therapeutics move past clinical trials and into large-scale manufacturing.

Some areas of biologics production are being hit harder than others. Many cell and gene therapy (CGT) companies have been impacted due to their complex manufacturing, delivery, and funding models [17]. In particular, cell therapy production has been impacted by delayed cell collection, reallocation of materials, and supply chain disruptions. In fact, one third of surveyed companies reported manufacturing delays, or a complete halt of operations, due to this disruption [17]. While the manufacture of gene therapies has been less affected by supply chain disruptions, the administration of both types of therapies in clinical trials is proving problematic; travel bans, delayed appointments, and prioritization of space for SARS-CoV-2 treatments are impacting both staff and clinical trial patients [17]. CGT products currently account for 12% of the pharmaceutical industry's clinical pipeline. With more than 750 CGT trials underway in almost 30,000 patients as of June 2020, clinical development will need to adapt to remain on track [18].

The new normal

A number of trends are expected to continue well beyond the crisis [1]. Some of these include:

- Accelerating the timeline for bioproduction optimization and scale-up
- Increased focus and demand for high-quality raw materials that meet required specifications
- Improving supply chain relationships
- Increased adoption of single-use technologies
- Process intensification with faster, overall smaller volume, and more cost-effective bioprocessing options
- Increased use of automation in processes, workflows, and analysis
- Increased outsourcing to contract manufacturing organizations (CMOs)
- Difficulty staffing talented workers as bioprocessing increases globally
- Regionalization outside the "major hubs"

Biopharma survey respondents believe that the trends of strengthening supply chains, regionalization, and outsourcing will all govern the new normal of bioprocessing [1]. The increased adoption of digital tools and automation should also help supply chains become more resilient to future disruptions. With significant investment in R&D, supply stockpiling, and facility expansions, the predicted trends should trickle down throughout the industry. Ultimately, SARS-CoV-2 infections may be the catalyst for accepting and promoting some of these emerging trends.

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The next normal

Despite the pressures being applied to biologics production, it is possible that by forcing rapid innovation in the bioprocessing industry we may quickly move beyond the new normal ushered in by SARS-CoV-2 infections, and into the next normal.

In April 2020, four of five pharma companies surveyed on the impact of SARS-CoV-2 infections predicted a significant increase in the demand for lyophilization and mRNA synthesis [19]. With multiple RNA-based COVID-19 vaccines in development and authorized for use, successful scale-up is demonstrating proof-of-concept for RNA *in vitro* transcription (IVT) platform technology. Scaling up these RNA IVT platforms will increase the need for enzymes and plasmid DNA production, which will ultimately lead to an increased demand in fermentation processes. Overall, this accelerated development will likely begin to speed up the progression of new, innovative therapies beyond SARS-CoV-2 infections [17].

Rapid innovations require rapid turnaround. Ensuring that supply chains are robust and sustainable will be essential as we transition into the next normal. Clinical trials and regulatory approval processes may also begin to shift, with complex protocols forced to be re-evaluated in order to shorten timelines and create the most efficient regulatory process possible.

Between shifting trends and rapid innovation, one thing is clear—the crisis due to SARS-CoV-2 infections has changed the mindset of biologics production for good.

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