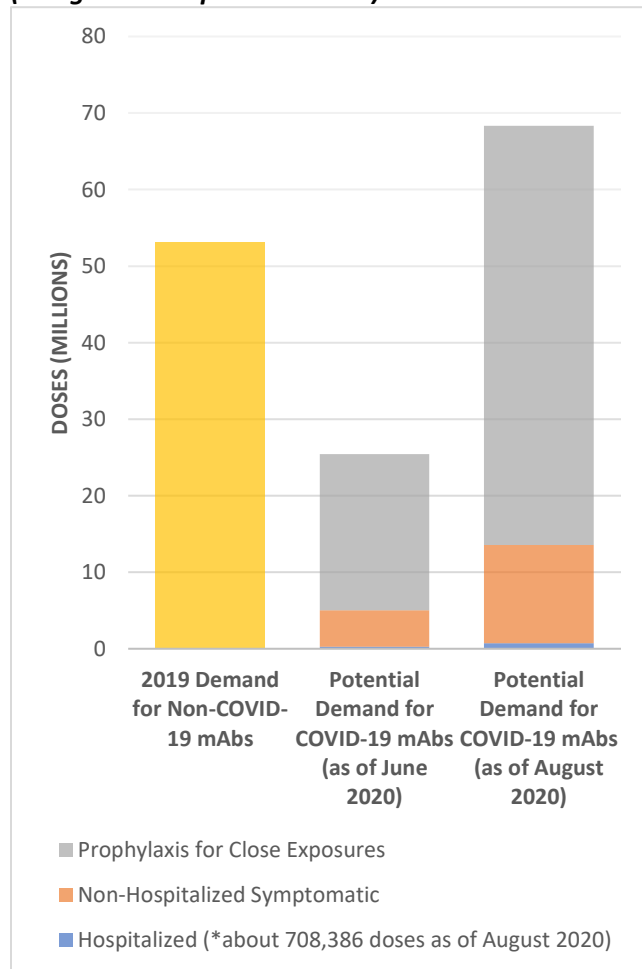


COVID-19 Manufacturing for Monoclonal Antibodies

Monoclonal antibodies (mAbs) offer the potential for effective treatments for COVID-19, before and even after a vaccine becomes available. In this issue brief, we estimate the demand for mAb drug products (COVID-19 and otherwise), an overview of the manufacturing process for mAbs, and an analysis of manufacturing capacity currently in use to make mAbs for the North American and European markets. We follow with a discussion of policy implications, with attention to manufacturing issues needed now to help assure adequate supply.

August 2020 Update

Potential U.S. Demand for COVID-19 mAbs (using current epidemic levels)¹



As of August 2020, we estimate that over the next year hospitalized patients would require 0.71 million doses of neutralizing mAbs, non-hospitalized symptomatic patients 12.8 million doses, and people with close exposure to confirmed cases would need about 55 million doses. This is more than a two-fold increase in every category since our last estimate in June 2020.

Introduction

Antibodies are produced naturally by the immune system to recognize components of disease-causing agents, such as bacteria, viruses, or cancer cells, and to mark them for destruction. Monoclonal antibodies (mAbs) can be created in the lab by recombinant DNA technology to mimic those antibodies naturally generated by the immune system. As a class, mAbs offer the potential for effective treatments that are well tolerated by patients.

Monoclonal antibodies in development to treat COVID-19 include both neutralizing antibodies, which can directly target coronavirus, and antibodies that can address acute respiratory distress syndrome, which takes place when the immune system overreacts to the COVID-19 infection and damages the lungs. Neutralizing antibodies have the potential to both treat and prevent COVID-19 infection.

Several mAb candidates to treat COVID-19 have entered human clinical trials and could be available more broadly to patients through emergency use authorization or fast-track approval in a matter of months. Even if there is a vaccine approved towards late 2020, inoculating hundreds of millions of Americans will take time. The vaccine may also be less effective for those with weaker immune systems. For these reasons, if clinically successful, mAb COVID-19 treatments will provide important therapeutic options not only until vaccines are developed but beyond.

This issue brief provides an estimate of the demand for mAb drug products (COVID-19 and otherwise), an overview of the manufacturing process for mAbs, and an analysis of manufacturing capacity currently in use to make mAbs for the North American and European markets.

Demand for mAb Drug Products

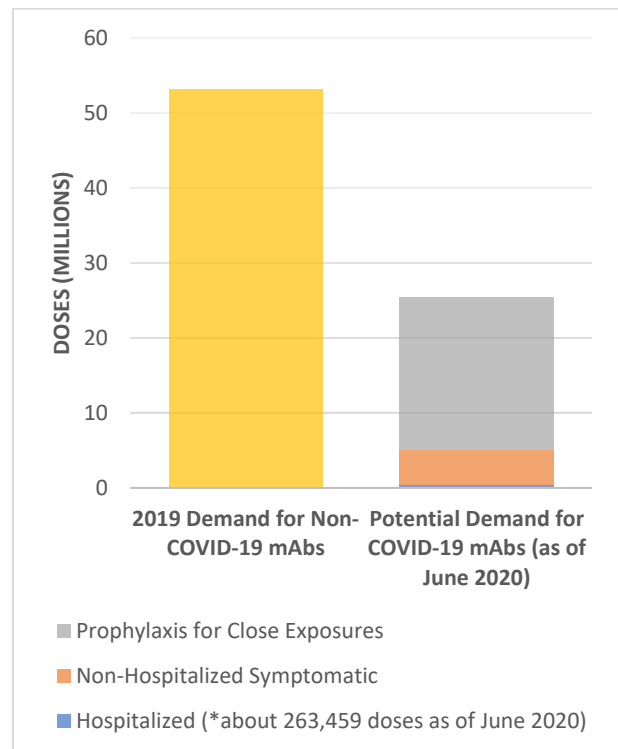
IQVIA estimates that approximately 53 million standard units (i.e., doses) of mAbs were sold in 2019 in the United States, many of which treat severe illnesses that address otherwise unmet medical needs: 39 percent were immunology products, 25 percent were oncologic products, and 9 percent were immunosuppressants, and 27 percent for a range of indications including pain, lipid regulators, respiratory agents, osteoporosis, and multiple sclerosis.²

These statistics provide an important context for the possible use of mAbs in preexposure and postexposure treatment of COVID-19. Here we assess the potential U.S. demand for COVID-19 mAbs using the market segments being tested for neutralizing mAbs:³ hospitalized patients, non-hospitalized symptomatic patients, people with close exposures to patients, and healthcare workers. Estimates for these latter two groups apply to neutralizing mAbs that would be administered as prophylaxis.

At current rates of infection, hospitalization, and symptomatic disease for COVID-19, and assuming only one dose is needed per patient,⁴

we estimate that over the next year hospitalized patients would require 0.26 million doses of neutralizing mAbs, non-hospitalized symptomatic patients 4.77 million doses, and people with close exposure to confirmed cases—defined conservatively as those in the same household as those who contract COVID-19—would need over 20 million doses. With infection and hospitalization rates increasing in the United States and with forecasts of a much more significant burden in the fall, these numbers are only a lower bound for what the true demand might be when a drug becomes available.

Potential U.S. Demand for COVID-19 mAbs (using current epidemic levels)⁵



Using mAbs as prophylaxis for frontline healthcare workers would further drive up demand. The number of frontline workers working with COVID-19 patients is unknown, but if we consider there are an estimated 13.8 million healthcare workers with direct patient contact⁶, the potential prophylaxis use for them could rival or even exceed that of close patient contacts if more than one dose per healthcare

worker were needed. Even if a substantial share of close contacts and health care workers are determined to be less likely to benefit from neutralizing antibody treatment, or if alternative prophylactics are available, demand is likely to be large relative to mAb manufacturing capacity.

While it is too soon to know exactly how much drug substance will be needed to meet the cumulative U.S. demand for neutralizing mAbs, we can conclude that, while it is feasible to meet the demand for treatment for hospitalized patients, any broader use of COVID-19 treatments would likely produce significant strain on manufacturing capacity that largely reflects only the ongoing demand for non-COVID-19 mAbs in mind.

Manufacturing of mAbs

To understand that extent to which manufacturing can be readily repurposed or expanded, it is helpful to understand how mAbs are manufactured.

Manufacturing of mAbs generally consists of upstream processes for production of the crude protein drug via cell culture in a bioreactor followed by downstream processes for purification of the bulk drug substance and formulation and sterile filling of the final drug product. The sterile-filling process is generally a procedure that is common among sterile injectable products. As such, it can be quite amenable to contract out to multi-product filling facilities.

In contrast, the fungibility of the mAb manufacturing capacity depends on the process mode and bioreactor type. Two popular bioreactor process modes are fed-batch and perfusion. Fed-batch is when the nutrient feed is added to the bioreactor during the culture process. Perfusion mode is also known as continuous and is where the nutrient feed is constantly replaced with a fresh supply. Fed-batch bioreactors currently dominate most of biomanufacturing due to their scalability and volumetric output.

Another aspect of fungibility is bioreactor type. Stainless steel bioreactors have historically been used for large-scale production, though single-use bioreactors have become more available in recent years due to the relatively short turnaround between batches (clean-up operations are quicker) and reduced upfront investment. Manufacturers specializing in one product generally tend to use stainless steel bioreactors, while single-use bioreactors are often used by contract manufacturers who produce a variety of different products.

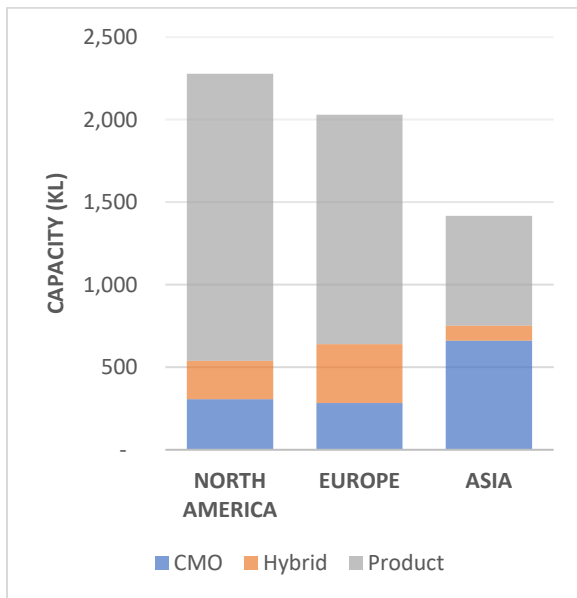
Setting up new manufacturing capacity takes time. Modular platforms are being stood up within 18 months,⁷ years shorter than for the traditional fixed facilities. However, the capacity of such platforms is also lower. Another alternative is restoring facilities no longer in use. However, the availability of such facilities and what it would take to restore them to operating status is unclear, and they are unlikely to be available in the short term.

Current mAb Manufacturing Capacity

In the short term, COVID-19 mAb manufacturing will need to rely on facilities either in use or in development. For this reason, we assessed current mAb manufacturing capacity using BDO's proprietary bioTRAK® database of biopharmaceutical products, which details facility-level bioreactor capacity for products used in North American and European markets, whether sold commercially or in preclinical development.

The bar chart below describes the expected mammalian cell bioreactor capacity either currently in use or available within the next 6 months, serving either North American or European markets. Spread across 200 facilities worldwide, total capacity is split between companies which employ an in-house manufacturing network (product), act solely as contract manufacturers (CMO), and those which employ a combination strategy by performing both in-house and contract manufacturing (hybrid).

Mammalian Cell Bioreactor Capacity for 2021⁸



Barring one small clinical facility in Canada, North America’s manufacturing capacity, equal to about 40 percent of the total bioreactor volume serving markets covered by bioTRAK®, lies within the United States. A large portion, or 78 percent, of that capacity is with manufacturers that only make in-house products.

Of the capacity displayed in the figure, 677 kL, or 12 percent, is not currently available but will be within the next six months. A bulk of this expected capacity, or 452 kL, is being developed in Europe, specifically in Switzerland and Ireland, largely by product manufacturers.

By January 2021, the U.S. manufacturing capacity is set to increase by only by 6 percent, with approximately half owned by contract manufacturers. A further 748 kL is currently expected to come online between 2022 and 2024, half of which will also be located in Europe. It is currently unclear to what extent development of at least some of these bioreactors can be advanced.

Policy Implications

It is possible that clinical trials for initial COVID-19 therapeutics could be completed in a matter of months, and there may be significant

demand for such therapeutics under emergency use authorizations even sooner. To meet the potential demand for these treatments, further steps will be needed to maximize the impact of limited production capacity towards the most promising candidates (such as mAbs) while still maintaining adequate supply of other biologics.

Our conversations with subject matter experts have identified two key areas that require attention. First, there is a need to address how to achieve maximal timely production of effective COVID-19 therapies given limited manufacturing capacity. Second, there is a need to quickly and flexibly move production between different facilities to maximize the availability of existing production capacity without creating shortages of important non-COVID-19 biologics.

Currently, manufacturers of COVID-19 therapeutics including manufacturers of neutralizing mAbs are largely making their own arrangements for sufficient manufacturing capacity. This creates several complications in the pandemic setting. First, manufacturers must take on financial risk to enable rapid availability when clinical testing is complete. As a result, it may be challenging for them to make large enough advance investments to meet potential needs, for example if the pandemic worsens by fall. Second, each manufacturer acquiring capacity in advance—what some industry experts described in interviews as “land grabs”—may create complications in matching limited available supply with the particular mAbs that demonstrate clinical effectiveness.

Absent government intervention, manufacturers might also work together on their own to reallocate their capacity to the most promising therapies as clinical evidence emerges. Indeed, it is in their financial interest to avoid losses on capacity investments on products that do not succeed. However, such collaboration on capacity allocation would need to happen quickly and based on accurate (and potentially confidential) product information. These collaborations would normally raise

serious antitrust concerns. To address such issues, the U.S. Department of Justice (DOJ) and Federal Trade Commission (FTC) issued a joint antitrust statement pertaining to COVID-19 guidance⁹ and have shown willingness to expedite business review letters.¹⁰ Despite that, it is not yet clear to what extent there is such industry coordination and how well it is working.

The federal government could play a coordinating role here, similar to the role government experts are playing in vaccine development. Operation Warp Speed has made substantial investments in advance manufacturing capacity for what Federal officials have judged to be the most promising vaccine candidates, where the scale and complexity of manufacturing is truly unprecedented.¹¹ Similar, perhaps more limited coordination and financial support could help avoid manufacturing shortages and mismatches for COVID-19 therapeutics. This could include assistance with anticipating issues in technology transfer and contractual arrangements among manufacturers, as well as provision of some financial support to provide additional manufacturing capacity if shortages are expected.

The second major area requiring attention is the need for manufacturing capacity to be activated to allow for the development of new COVID-19 mRNA products, without disrupting the availability of the critical treatments that patients rely on. For example, while efforts have focused on making the best possible use of existing manufacturing capacity, it may be feasible to expand manufacturing on a relatively short timeframe using replicate single-use modular platforms or by identifying and bringing online mothballed facilities.

Another option may be creating financial incentives or other support for greater production and storage of non-COVID-19 drugs, so that more manufacturing capacity is freed up when an effective COVID-19 therapy is ready to launch.

As such manufacturing shifts occur, regulators and manufacturers will need to work hand-in-hand to ensure that product transition, scale-up, and process validation steps can occur quickly and safely across multiple facilities.

Considerable policy attention has focused on advance planning for manufacturing capacity for vaccines. This issue brief suggests that although mAbs and other potential COVID-19 therapeutics do not require as much advance planning or vaccine-level manufacturing scale, additional policy attention is needed now to assure that shortages will not emerge as more therapeutics demonstrate effectiveness against the pandemic.

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Disclosures

Mark B. McClellan, MD, PhD, is an independent board member on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and Seer; co-chairs the CEO Forum for the Health Care Payment Learning and Action Network; and receives fees for serving as an advisor for Blackstone Lifesciences, Cota, and MITRE.

¹ Graph of estimated demand for neutralizing mAbs in three patient groups compared to the 2019 US mAb units produced. Healthcare workers were excluded from this graph for reasons of scale.

² Data courtesy of IQVIA.

³ Regeneron's REGN-COV2 is one such example.

⁴ [COVID Tracking Project data](https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html);
<https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html>;
<https://www.acpjournals.org/doi/10.7326/M20-1874>

⁵ Graph of estimated demand for neutralizing mAbs in three patient groups compared to the 2019 US mAb units produced. Healthcare workers were excluded from this graph for reasons of scale.

⁶ Himmelstein and Woolhandler, "Health Insurance Status and Risk Factors for Poor Outcomes With COVID-19 Among U.S. Health Care Workers," *Annals of Internal Medicine*, April 2020.

<https://www.acpjournals.org/doi/10.7326/M20-1874>

⁷ GE Healthcare [press release](#), June 2016.

⁸ Data courtesy of BDO.

⁹ DOJ, FTC. [Joint Antitrust Statement Regarding COVID-19](#), March 2020.

¹⁰ See for example the April 2020 business review [letter](#) to AmerisourceBergen.

¹¹ HHS. [Operation Warp Speed Factsheet](#), June 2020.