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Monoclonal antibody therapies for COVID-19: lessons learned and implications for the development of future products[☆]

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Several companies were authorized to treat COVID-19 patients with monoclonal antibodies within 1–2 years of the start of the pandemic. These products were discovered, developed, manufactured, clinically tested, and approved under emergency-use authorization at unprecedented speed. Pandemic urgency led to novel development approaches that reduced the time to clinical trials by 75% or more without creating unacceptable patient or product-safety risks. Hundreds of thousands of patients now benefit from these therapeutics that have reduced the rates of hospitalization and death. The chemistry, manufacturing, and control development strategies set a new precedent of speed, safety, and demonstrated clinical benefit and will likely have a lasting impact on the development of future monoclonal antibody therapies for not only infectious diseases but also for oncology, inflammation, and rare diseases.

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Introduction

Monoclonal antibody (mAb) therapies for treatment of patients with COVID-19 have been launched at an unprecedented pace by multiple companies, delivering

clinically meaningful interventions since 2020 [1]. Emergency-use authorization (EUA) has been granted by many countries in record-time allowing hundreds of thousands of patients to benefit. What was once an audacious goal and medical imperative to develop and deliver mAb therapies early in the pandemic has now come to pass [2]. This review will share experiences from our COVID-19 journey at Vir Biotechnology and GlaxoSmithKline and include perspectives from other companies that have been shared publicly.

This is an amazing achievement for the pharmaceutical industry and regulatory health authorities and speaks to the maturation and broad acceptance of mAbs as therapeutics. Without question, delivering these mAbs in record time was only made possible by the industry convergence on mAb platform processes and each company's existing manufacturing networks [3]. This review will share experiences from our COVID-19 journey at Vir Biotechnology and GlaxoSmithKline to develop sotrovimab and other antiSARS-CoV-2 mAbs and include perspectives from other companies that have been shared publicly in nearly two years since the COVID-19 pandemic began. As we look ahead, we will consider how will these experiences catalyze changes to the development of future mAb products. Informed by 25 years of production history [4] and approval of over 100 licensed mAbs [5], we will discuss the implications our chemistry, manufacturing, and control (CMC) development strategies for COVID-19 mAbs may have for development of future mAb products.

COVID-19 monoclonal antibody therapeutics-development overview

A profile of the COVID-19 mAb products receiving EUA through late 2021 is provided in [Table 1](#) [1]. Seven mAbs from four companies received authorizations in the United States [6] within 10–24 months after the start of the pandemic [7–16]. These products have been approved for early treatment of COVID-19 patients and some are also being studied for prophylaxis and hospitalized patients. Many more mAbs are under evaluation for treatment of COVID-19 [17]. In light of the global scale and medical urgency of the COVID-19 pandemic, mAb design, de-

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Table 1

COVID-19 mAb products authorized in the United States by Jan 1, 2022.

Monoclonal antibody	Sponsor	Monotherapy or cocktail	Route of administration	Dosing regimen
Bamlanivimab Etesevimab	AbCellera and Lilly	Cocktail	IV infusion	2100 mg
Casirivimab Imdevimab	Regeneron and Roche	Cocktail	IV infusion SC injection	1200 mg
Sotrovimab	Vir and GlaxoSmithKline	Monotherapy	IV infusion IM pending	500 mg
Tixagevimab Cilgavimab	AstraZeneca	Cocktail	IM injection	600 mg

velopment, and formulation strategies have been essential to ensuring timely patient access to these therapies.

Design

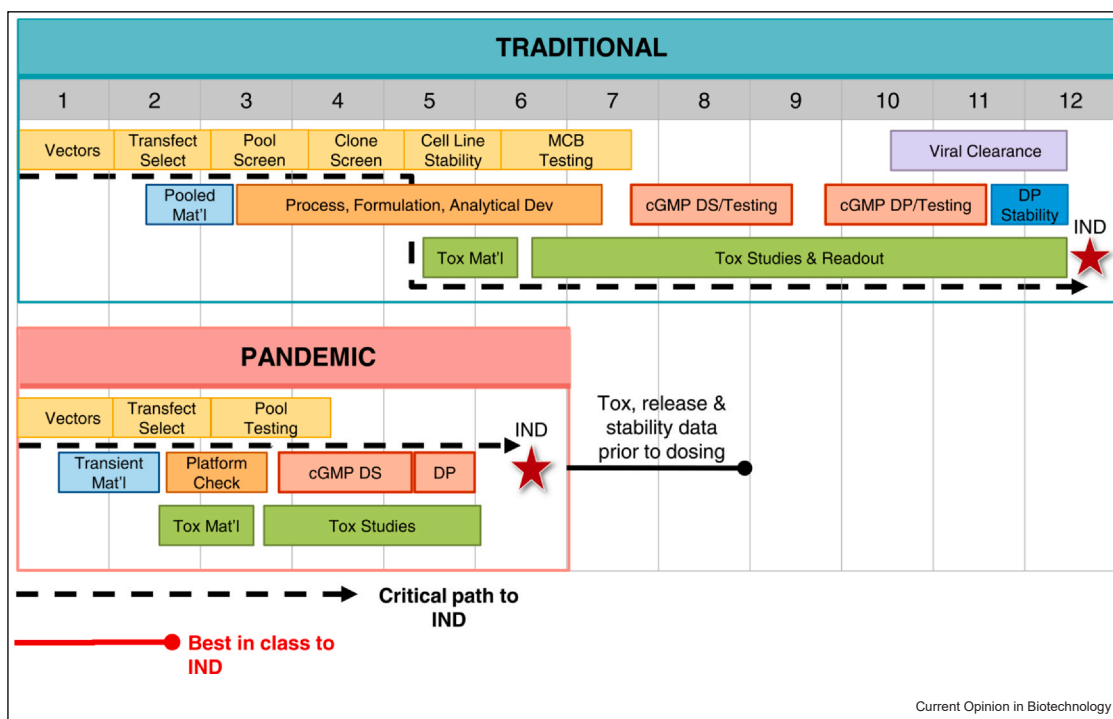
The COVID-19 pandemic has magnified the importance of COVID mAb selection and design. COVID-19 mAbs are being produced by the ton, representing the greatest combined annual mAb production for a therapeutic indication ever [18]. Because production capacity for mAbs is not unlimited, dosage requirements and monotherapies versus cocktail regimens have significant implications for being able to deliver sufficient volumes of mAbs for global launch and supply. Indeed, the large pipeline of multiple COVID-19 mAbs being developed,

manufactured, and launched in such relatively rapid succession has constrained both worldwide production capacity and raw material supply; > 12-month lead times are common for obtaining additional capacity and obtaining a number of common-platform raw materials and components. Highly potent mAbs have advantages in lower production capacity requirements and ease of patient administration, with other potential benefits gained by protein engineering for extended circulatory half-life or modulated effector function [9,19–22].

Development

Figure 1 compares the development timelines for a traditional mAb (approximately 12 months from gene

Figure 1



mAb development at pandemic pace. The timeline to phase-I clinical studies using mAb therapeutics for pandemic outbreaks can be significantly accelerated without heightened product-safety risks compared with current practice. Several levers can be combined to streamline activities by accepting more business risk.

Box 1 Key take-aways.

- Multiple companies are authorized to treat COVID-19 patients with monoclonal antibodies (mAbs)
- They were discovered, developed, manufactured, tested, and approved at unprecedented speed
- Hundreds of thousands of patients around the globe benefit from these therapeutics
- CMC strategies for these mAbs may have a lasting impact on the development of future mAb therapies

Box 2 Levers to accelerate early-stage mAb development.*Cell-line development.*

- Use high productivity host, consider targeted integration
- No pool screening
- Abbreviated cell line stability for clone selection
- MCB into current Good Manufacturing Practice (cGMP) production concurrent with bank testing

Process development.

- Large-volume transient material supply
- Platform check (minimal process, formulation, and analytical development)
- Modular viral clearance — no studies
- Abbreviated tox studies off critical path

Manufacturing and stability.

- Tox lot using a pool of cells or clones
- DS and DP conditional release
- Minimal cGMP DP stability for IND

synthesis to Investigational New Drug application (IND) as current benchmark of best-in-class) and COVID-19 pandemic mAbs (6 months or even shorter). The acceleration was achieved with multiple CMC levers (Figure 1 textbox) that streamlined production of the clinical trial material (CTM) for first-in-human studies. Using these strategies, several companies initiated COVID-19 clinical trials quickly (50–70 days), many months faster than a mAb for treatment of nonpandemic diseases [12,23]. Some of the companies reported that this was enabled by producing the CTM using a stable pool of transfected host cells rather than clonal cell lines [24–27]. In these cases, clonally derived cell lines were also established immediately afterward, subsequently banked, and material produced from these cell banks was subjected to a comparability assessment to the initial CTM batches produced from stable pools. This strategy is analogous to using stable cell pools for production of preclinical toxicology studies, which became commonplace several years ago [28–31]. The concept of biased selection of the final clone for its ability to produce CTM that is highly comparable to material used in toxicology studies or first-in-human trials to minimize product comparability risk applies in both cases. Proactive engagement with multiple health authorities established confidence in this ‘pool for clinic’ strategy. Should this approach be the future of cell line development? Given that the time savings are a month or two at most, it should probably not be a new development standard but rather reserved for extremely urgent and unmet medical needs, including future pandemics (Boxes 1 and 2).

Formulation

Three COVID-19 mAbs were launched as intravenous infusions, enabling a lower product concentration in the drug product vial and reducing the risks of product stability challenges. Some companies evaluated more convenient intramuscular or subcutaneous dosing, in some cases enabled by a higher concentration drug product (DP) or coformulated mAb cocktails [32]. A fourth COVID-19 mAb was launched using intramuscular administration, thus saving the complications of establishing a second route of administration. Full product expiry could not be supported by long product-specific stability studies, but was supported by platform knowledge and reliance on typical excipients, pH targets, storage conditions, and containers. Many mAb DP liquid formulations are stable for two years or longer, presenting a relatively low (but not zero) risk of significant stability issues.

Early-stage/late-stage development strategy and implications

The process and product development efforts leading to the initial IND for sotrovimab were conducted in less than five months. This necessitated parallel at-risk work on early- and late-stage development and avoided sequential activities gated to key milestones. The IND filing, the commercial process and product configuration lock, and process characterization initiation all took place over three successive days in the summer of 2020. The strict adherence to our contract development and manufacturing organization’s (CDMO’s) mAb process

platform did not allow for optimization of the process, formulation, or analytics, but rather an acceptance of ‘acceptable to proceed’, given that no product quality, stability, or process robustness issues were observed.

The scale-up to commercial production was initiated using the CDMO’s platform knowledge. The GlaxoSmithKline (GSK) team rapidly started a commercial-scale production campaign at our CDMO moving directly from a small number of at-scale drug-substance (DS) cGMP that runs directly into the process performance qualification (PPQ) campaign. PPQ batches were tested with qualified methods and analytical method validation was performed concurrently with PPQ runs. The prePPQ DS runs were underway before process characterization was complete, and the associated potential business risks of initiating the PPQ before completing this work were weighed and accepted in light of the pandemic. The initial control strategy was established using a risk assessment that enabled process characterization studies to focus on critical and key parameters. These prePPQ runs also accelerated the DP PPQ runs rather than waiting for complete results from DS PPQ work. Although this is not a universal process validation approach today, perhaps, it should become a general approach for future products in that it avoids significant preinvestment in process characterization studies before the gating readout of clinical milestones.

This strategy benefits greatly from the ‘proven path’ between process development and manufacturing sites or partners and from colocated DS/DP manufacturing and analytics, and from well-established relationships between partner companies. The pandemic necessitated new partnerships and supply chains for a number of companies, and it is telling that several companies simultaneously transferred their COVID-19 mAb DS and DP manufacturing processes to multiple facilities within 3–6 months [33]. This dramatically upends industry’s acceptance for tech transfers of a typical 12+ month timeline and is a challenge to future performance expectations.

The full package of process characterization and validation (PC/PV) used to support the EUA filings was conducted by the Vir/GSK team and CDMO partners in six months and included all typical studies, including demonstration of unit operation and analytical method robustness, acceptable limits of in vitro cell age, resin reuse, and virus clearance capabilities. The EUA filing was completed within three months of completing the DS PPQ lots. In the future, viral clearance claims based on modular studies for robust unit operations such as pH inactivation and virus filtration should also be considered. Other unit operations such as protein A chromatography, flow-through anion-exchange chromatography, and final ultrafiltration/diafiltration should be classified as low-risk

steps that can build on platform- process information and prior knowledge [34], different than the cell-culture production that can vary with individual cell lines. The DP process and configuration were also supported by platform knowledge using common equipment, vials, and established inspection techniques.

Regulatory strategy and implications

A small number of sotrovimab DS and DP at-scale cGMP lots comprised the basis for assessing commercial process capability at the time of our EUA applications. The number of unique lots used for clinical studies was also small. Consequently, we set the release and stability specifications with appropriately wide ranges based in part on platform knowledge with the expectation that these specifications will be reviewed and potentially revised after further manufacturing experience (including bringing on additional manufacturing facilities).

While we were unable to achieve a global release control strategy given different expectations of health authorities, our strategy demonstrated the flexibility provided by the health authorities and acknowledged both the importance of platform knowledge and the need to mitigate product supply risks for life-saving therapies.

Other examples of this flexibility included:

- A cell-based bioassay was not fully validated at the time of our EUA application, but there was a commitment to switch over from the launch bioassay as soon as possible [35]; a surrogate enzyme-linked immunosorbent assay (ELISA) technique was used in the interim.
- New stability data were provided during the review as soon as they became available.

The unique circumstances of the COVID-19 pandemic have highlighted other areas where health authorities can also facilitate faster global access to mAb therapeutics. COVID-19 mAbs were launched in global markets almost simultaneously at lightning speed, unlike the typical multiyear period for a sequential rolling launch of mAb therapies. An attractive future state would achieve the global regulatory harmonization efforts that remain elusive and coordinated reviews among multiple health authorities would reduce the workload for both innovator companies and health authorities. Health authorities can also help mitigate production delays due to shortages of key raw materials, which is perhaps the greatest constraint many companies face in ramping up volumes quickly to supply the highly uncertain product-demand requests from governments and the private sector. Some companies have dual-sourced key raw materials, resins, and membranes (e.g. chromatography resins, virus removal filters, and depth filters) upfront to ensure continuity of product supply. Providing industry guidance on the data

and type of risk-based assessment needed at the time of application submission to support dual sourcing of critical materials would ensure more robust and resilient product supply chains [36].

Early in the COVID-19 pandemic, it was recognized that the demand for antiSARS-CoV-2 mAbs would likely outstrip the available manufacturing capacity [37] and given the large COVID-19 mAb pipelines and widely uncertain demand scenarios, companies quickly locked up all available, short-term (2020–2022) large-scale CDMO mAb capacity. Recognizing the importance of industry coordination to mitigate these capacity distortions, several companies have been allowed by the U.S. Department of Justice to exchange manufacturing-related information with a goal of increasing overall output of COVID-19 mAbs [38]. Having the US Government (USG) fund, track, and help coordinate a few strategic partnerships between innovator companies holding significant internal capacity and one or more large CDMO (s) well in advance of an emerging pandemic would be a sound investment. Some of the USG infrastructure is already set up as HHS established a Supply Chain Control Tower in March 2020 “to provide visibility into critical medical supply chains to support U.S. Government decision-making and actions on planning, acquisition, prioritization, allocation, and targeted distribution to get supplies where they are needed” [39]. A precedent has also been set as there are multiple industry clinical and commercialization collaborations brought about by the COVID-19 pandemic, including Vir/GSK and Pfizer/BioNTech. In the CDMO industry, the COVID-19 pandemic accelerated plans to add additional capacity, with investments by at least four large CDMOs for DS manufacturing bringing nearly half-a-million liters of new mammalian cell culture capacity online by 2025, most of it collocated with DP manufacturing. While a fully configured manufacturing consortium [40] may be difficult to assemble, the COVID-19 pandemic has helped build the collaborations and supply chain infrastructure (including raw material manufacturing capacity) that can be leveraged for future pandemics.

Further upstream, the USG initiative to transform the United States’s pandemic- preparedness capabilities aims to “fundamentally transform its ability to prevent, detect, and rapidly respond to pandemics and high consequence biological threats” [41]. Funding mAbs with promising characteristics for neutralizing influenza or other diseases with pandemic potential [42–45] through cell line development, process development, and clinical manufacturing would create a national stockpile of product candidates that would be available early during a pandemic to quickly initiate clinical studies. This advanced investment would provide protection for healthcare providers, emergency-service workers, and mission-critical personnel for national security.

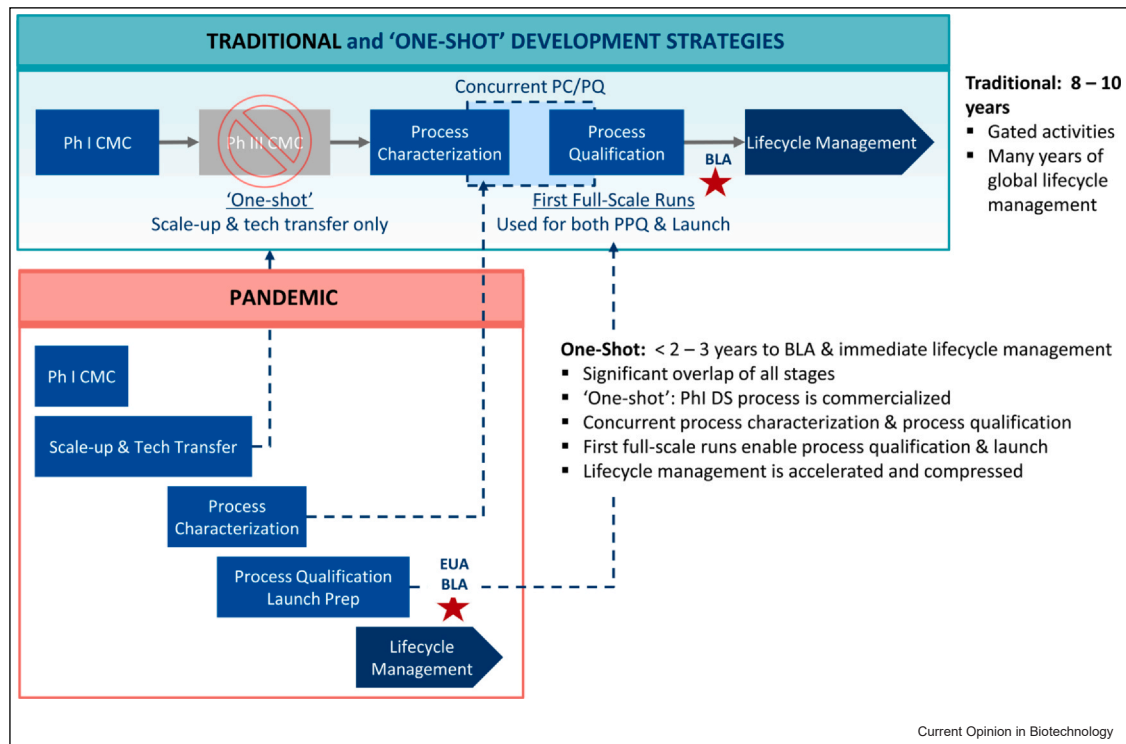
While stockpiling liquid DP in such a health-security pharmaceutical pipeline would be simpler and enable higher production capacity than lyophilized DP, the shelf-life would eventually be exceeded, and new material would need to be made. Storing frozen DS would be a better option since it is typically stable for many years but would also require reserved capacity at a high-volume DP facility for rapid conversion. Advanced collaborative manufacturing partnerships noted above would also potentially address capacity, timing, and raw material limitations.

Much has been written about novel manufacturing technologies or alternate production hosts for mAb production [46–48], but these would not seem well-suited to support pandemic preparedness. A new manufacturing network would add cost, complexity, and risk, and would not be as ‘battle-tested’ as the COVID-19 mAb innovator and CDMO companies that have delivered ton-quantities at such a rapid pace. Some believe that the conventional mAb manufacturing platform using large-scale fed-batch mammalian cell production, chromatography, and filtration unit operations is outdated and advanced manufacturing innovations are needed to decrease costs and cycle time [48–51]. Table 1 lists four companies who have authorized seven mAbs in just 1–2 years with volume and quality; this is compelling evidence that current, proven technology is a reliable approach to creating robust product supply. This was only possible due to mAb production technology having advanced sufficiently to deliver several g/L titers reliably on ‘one-shot’ development strategies that have a high probability of success. If the COVID-19 pandemic had struck in 2000 and not 2020, it would not have been possible to meet the global needs for therapeutic antibodies.

Development strategy for future monoclonal antibody therapies

The COVID-19 pandemic caused many of us to rethink traditional process development paradigms and recalibrate our tolerance for business risks related to development and manufacturing to hyperaccelerate the development timeline as shown in Figure 2. Having demonstrated multiple companies can go from gene-to-IND in less than 6 months, what did we learn? All COVID-19 mAbs essentially used a ‘one-shot’ development strategy for fast time-to-clinic rather than traditional, sequential early- and late-stage development where process or formulation changes are introduced before pivotal clinical studies. A high titer early phase cell culture process using a well-established CHO cell line coupled with robust process and formulation platforms requires no changes for late stage, engenders minimal questions of product comparability, streamlines product development, reduces investment before pivotal

Figure 2



Next-generation mAb development. Three different strategies for the lifecycle of mAb-product development are shown for traditional, pandemic, and future 'One-shot' programs. The traditional strategy is sequential with gates determining the start of the next phase of CMC development. The pandemic strategy required rapid Ph I development, extreme timeline compression, and overlaps between phases and accepting business and financial risks. The 'One-shot' strategy brings three pandemic elements into the traditional timeline to accelerate and streamline development for standard mAbs.

trials, and potentially keeps CMC off the critical path to licensure. If DP configuration changes are desired, they could be decoupled from DS-process changes and potentially be started earlier. The industry's COVID-19 experience demonstrates that mAb process and formulation development has matured to a point where a 'one-shot' development is a viable strategy for all products developed with a strong platform and production knowledge base.

Another change to traditional development approaches targets PC/PV activities. For process characterization activities, not requiring these studies be complete before process- performance qualification helps delay this significant resource investment by a year or more, and yet can still be scheduled to ensure the necessary information is complete for a license application, including the identification of critical process parameters and their appropriate control ranges, and a justifiable product control strategy and release specifications. For process validation activities, several COVID-19 mAbs moved directly from 'one shot' development to a combined PPQ/product launch manufacturing campaign to produce sufficient quantities of product for global supply

(Figure 2). Routinely using this strategy would minimize the number of full-scale runs and investment before launch by eliminating separate Ph III and PPQ campaigns. In one aggressive embodiment, the very first cGMP batches could be produced in the launch facility at full-scale and be part of the PPQ lots.

Conclusions

From the start of the COVID-19 pandemic in January 2020 through December 2021, multiple companies delivered significant quantities of mAb therapies to COVID-19 patients, reducing hospitalization rates and saving lives. The quality, safety, and stability of these products reflect the maturation of the biopharma industry to develop and commercialize mAbs since the licensure of the first recombinant mAb (rituximab) in 1997. The companies that brought these COVID therapies to market accepted business risk and early investments but did not compromise product quality or accept safety risks. Now, this class of products has been made available at unprecedented speed, and scales leveraging-platform processes and global manufacturing capacity at existing CDMOs and innovator companies. Given this 25-year history of recombinant mAbs as

established therapies, we propose that the product quality, process development, and manufacturing risks associated with recombinant mAb therapies are now so well-understood that we can more broadly accelerate first-in-human studies and subsequent product commercialization for future indications. Patients in all disease areas are waiting.

Conflict of interest statement

Kelley, Douglas, Renshaw, and Traviglia work at Vir Biotechnology, Inc.

Data Availability

The data that have been used are confidential.

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