The Covid-19 Pandemic – How to Create Manufacturing Capacity for the Best Candidates





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Abstract

This second article, in a series dedicated to the Covid-19 Pandemic and related Global Pharmaceutical Manufacturing Challenges. The first article discussed the different treatment and vaccine technological options and their feasibility. This article will estimate the scale of global manufacturing capacity that may be required to keep pace with the clinical trials, and subsequent mass production, for the various drug treatment and vaccine options currently being pursued by the industry. Short- and long-term capacity requirements are estimated and compared to existing extrapolated capacities. The specific facility design requirements for various pharmaceutical intervention options are discussed in order to assess the relative complexity of options available for ramping up global capacities with unprecedented urgency. Additionally, some advantages and disadvantages of retrofitting existing facilities versus building new greenfield facilities are presented.

Keywords: Covid-19, pharmaceutical, biopharmaceutical, capacity, vaccine, treatment, manufacturing

1. Introduction

Despite the current public strategies to suppress new Covid-19 infections by social distancing, personal hygiene and public space closures, it remains reasonable to assume that the total global infections (confirmed and unconfirmed) will reach 500 million by the end of 2020, leaving 7 billion people vulnerable to infection.

In the short term, the first line of defense - which thankfully carries limited risk - is the use of the naturally occurring anti-body immunoglobulin (IG), purified from human donors that have fully recovered from the disease. These anti-bodies will provide temporary protection from the virus and should be reserved initially for healthcare professionals and other critical service workers. The logistics of collecting, purifying and administering human blood plasma IG are cumbersome and ultimately limit the potential availability of this treatment for a large population. This temporary protective treatment depends upon people who have been infected generously donating their blood plasma on a periodic basis in a high

demand environment. This treatment is unfeasible as a primary or long-term solution for a pandemic.

The medium-term response to the pandemic is focused on mitigating and alleviating the most severe symptoms in patients. It is expected to include testing for Covid-19 indications and increased production of existing products, as well as development of new treatment agents that are proven to be effective, or aid in the recovery of the critically ill patients. The primary pathways to mortality that have been identified include severe lung and organ damage, secondary infections from a suppressed immune system and a cytokine "storm" caused by an over-activated immune system. Each of these pathways provide a potential mode of treatment for drug development. Current drug development approaches include existing and new anti-viral small molecules, viral replication inhibitors, engineered anti-bodies, immuno-suppression mAbs and immuno-stimulation mAbs.

The ultimate long-term response to the pandemic may be a prophylactic vaccine. A wide range of vaccine technologies are available to tackle this task. The technologies include traditional virus vaccines, advanced sub-unit vaccines and cutting-edge DNA and RNA vaccines. Traditional vaccines rely on either live attenuated or inactivated whole virus to elicit an immune system response. More recent technologies use a smaller single protein subunit (expressed from mammalian or bacterial cultures) to generate the immune response. The protein can be based on recombinant proteins, synthetic peptides, virus-like-particles or viral vectors. The third, and most recent, vaccine technology utilizes DNA or RNA to elicit protein manufacture in cells that mimic the antigens of the viral disease and thereby produce an immune response. Like the subunit technology, DNA and RNA technologies require mammalian or bacterial cultures to manufacture these vaccines. A frequent issue with the development of vaccines is that they can require a complicated formulation, involving one or more adjuvants, to increase effectiveness. The development of this formulation takes time, presenting the possibility that a first-generation vaccine may show sub-optimal effectiveness. A resultant need for larger and/or multiple doses would significantly impact the ability of the industry to provide a vaccine in quantities that could enable a global herd-immunity.

This article discusses and evaluates potential options for the short, medium, and long-term expansion of production capacity for Covid-19 drug treatments and vaccines. The key objective of the evaluation is to determine feasible and viable technology options that could offer the shortest production ramp-up timelines to the required scale, thereby bolstering public health to allow lifting of current social and travel restrictions.

There are additional challenges that, once a vaccine is developed, must be addressed. Notably, extensive world-wide testing will also be required for the understanding and control of this disease, not to mention the manufacturing and distribution of mass quantities of testing kits. Furthermore, vaccine hesitancy - declared by the WHO as one of the top ten threats to global health in 2019[i] - is also a factor in limiting the spread of the SARS-CoV-2 virus. While these issues can impact the course of this pandemic, they require separate specialties and expertise, and will not be addressed in this article.

2. Manufacturing Objectives: Treatments

The rapid development, clinical testing and regulatory approval of any treatment will be a formidable challenge. But there are signs that the industry, with conditional support and encouragement from the major global regulatory agencies, may manage to get approval of the new indication for the existing treatments, as well as new treatments and vaccines, in record time. An antiviral treatment, Remdesivir, has already received two limited approvals, with the requirement for additional clinical studies to continue in Japan[ii], or for compassionate use in severe cases in the U.S.A.[iii]. Many other treatments are already in clinical trial stages 2 or 3, with the manufacturers targeting approvals ranging from Q3 2020 to Q1 2021.

As of going to press, 1st June 2020, over 6.2 million people, of a global total of 7.8 billion people, have confirmed Covid-19 infections, resulting in at least 360,000 deaths, and only 40.6 % of patients so far are confirmed recovered[iv]. The number of Covid-19 infections before 2021 has been predicted between 153 million to 1 billion world-wide, with a median at 496 million[v]. Current data suggests that 5 % of the cases are critical, requiring intensive care, while 14 % of the cases are severe, requiring hospitalization[vi]. This means that 68 million people may require hospitalization, and would benefit from treatment. As discussed in the first article, several different treatments will be required, depending on which symptoms present in a patient; some will require immune response boosters, but others will need immunosuppression treatments.

Immunoglobulin appears to be a reliable path forward, with its predicted efficacy, and is expected to obtain approval in the coming months. However, production of immunoglobulin will be limited by the quantity of plasma that can be collected from people recovered from confirmed cases of Covid-19. The capacity to handle this manufacturing requirement in existing facilities is discussed in more detail in the Section 5.1.

Gilead, who manufacture Remdesivir, have announced they will be able to produce more than 1 million treatment courses by December 2020 and several million treatment

courses in 2021, if required[vii]. This is still only a fraction of the 68 million people that may require treatment. If malaria-type treatments prove to be effective some stockpiles of these drugs already exist (including the WHO), and there may be a large manufacturing capability available since they are produced by multiple companies.

Patients experiencing severe complications including acute respiratory distress syndrome, and requiring intensive care, can benefit from anti-inflammatory treatments to calm the inflammatory storm and reduce mortality. It is estimated that patients need 400 mg to 1,200 mg of the correct therapeutic protein[viii]. Assuming low range titers during fermentations, typical for products developed 20 years ago (1 g/L range), the total installed bioreactor capacity required to meet this need is in the order of 200,000 L. That would require, for example, Roche to use the full capability and maximal throughput of their largest manufacturing plant and dedicate that facility solely to the manufacture of this hypothetical protein product.

3. Manufacturing Objectives: Vaccines

Vaccines are being developed and tested at unprecedented speed, with some companies such as Moderna predicting approval before the end of this year. Other companies such as Johnson & Johnson have targeted their vaccine to be approved for emergency use by the beginning of 2021. Many others have stated a target date some time in 2021 for an approved vaccine, a heretofore unprecedented accomplishment as outlined in the previous article. In order to get understanding of the scale of the monumental manufacturing challenge to manufacture sufficient vaccines doses we present an analysis of the potential numbers involved.

Some initial studies have suggested that herd immunity for this virus can be achieved at approximately 70 % population coverage[ix]. Some viruses require over 90 % population coverage immunity for effective herd immunity. Taking into account that only a small fraction of the population has already contracted and recovered from the virus, this would mean that 5 billion doses for the world population will be required before herd immunity is reached, assuming that a single dose is sufficient. Depending on the vaccine, it is possible that multiple injections may be required to achieve sufficient blood antibody titer for effective immunity. In addition, it is likely that booster shots will be required to retain that immunity. There could be an ongoing need for billions of doses per year to maintain worldwide immunity.

In terms of market opportunity, a recent analysis by Morgan Stanley[x] determined that these requirments could lead to a Pandemic Markety of $10 – 30 B. They also suggest there is an ongoing endemic opportunity of $ 2 – 25 B, a market valuation that would be strong justification for considerable investment in successful Covid-19 vaccines.

How do these vaccine requirements line up with what manufacturers plan to produce? Johnson and Johnson plans to add capacity to make more than 1 billion doses of the vaccine available globally on a not-for-profit basis[xi]. Sanofi has announced it plans to produce 100 – 600 million doses of a recombinant vaccine using existing production capacity and has set a goal to extend manufacturing capacity to produce more than 1 billion doses in 12 months[xii].

In addition, Sanofi is working on an mRNA vaccine, targeting approval as early as the second half of 2021 and a production of 90 – 360 million doses by the first half of 2021. Pfizer and BioNTech SE are developing an mRNA vaccine. Their plan is to produce millions of doses by the end of 2020, subject to the success of the development program and the approval of regulatory agencies. They plan to rapidly scale up to capacity to produce hundreds of millions of doses in 2021[xiii]. Moderna is also developing an mRNA vaccine and has targeted approval before the end of 2020. They plan to initially use Lonza manufacturing facilities in the US and Switzerland and hope to begin batch production at the U.S. site as early as July of this year. By continuing to expand manufacturing sites, Moderna's capacity may reach up to 1 billion shots per year[xiv].

mRNA vaccines are based on DNA/RNA plasmids which are a challenging new technology. A typical mRNA vaccine may be a 100 µg dose, but requires multiple doses over a several week period. Currently the drug substance batches are only at the single gram scale, with a projected scale-up to 1 kg batches by the end of 2020. At this scale, the manufacturing technology would support 10 million doses per batch. But this will require the successful 1000-fold scale up of a new technology and still require a 100 successful batches per billion doses of vaccine.

The Serum Institute of India (SII) is an industry leader in vaccine manufacturing for Asia and the developing world. It is planning to manufacture several different vaccines. The first one is a non-replicating viral vector vaccine developed by Oxford University. A second live-attenuated vaccine is being developed for SII by Codagenix US, while the third vaccine is a recombinant vaccine developed by SII itself. SII has an estimated extra capacity of 400 – 500 million doses and aims to produce 20 – 40 million doses per month from September 2020[xv]. Bharat Biotech may also be a significant supplier of vaccines. They announced a partnership with FluGen and the University of Wisconsin-Madison to make almost 300 million doses of a vaccine for global distribution[xvi].

These examples of ongoing initiatives illustrate the order of magnitude required in vaccine manufacturing capacity. It

demonstrates that no single initiative or organization will be able to meet the world demand. Considering that not all vaccine development programs will be successful, and booster shots may be required, it is clear that even with these initiatives, there remains a significant production challenge in vaccination for herd immunity.

As a society, we should plan for manufacturing capacity that covers treatment requirements and best-case vaccine scenario, ideally supporting long-term worst-case scenarios. However, the longer term response will most likely need to be adjusted when more data becomes available in the coming months.

4. What Types of Facilities are Required?

Immunoglobulin (Ig) is produced in standard plasma fractionation facilities. Existing facilities have the required design and can be scheduled to produce Ig. The production of synthetic drugs such as malarial or anti-viral drugs is performed in a chemical reactor vessel. Existing manufacturing facilities for synthetic drugs will most likely be able to manufacture the Active Pharmaceutical Ingredient (API) without prohibitive levels of retrofit.

Biotherapeutics and most vaccines require standard cell culture and purification unit operations such as depth filtration, chromatography and diafiltration. Single use technology is readily available for these unit operations. The specific design of a manufacturing facility for a vaccine will depend on the type of vaccine.

Non-viral type vaccines – recombinant vaccines, plasmid DNA and mRNA – are based on standard fermentation processes. Recombinant vaccines – non-viral vaccines that use eukaryotic cells for fermentation – could use existing cell culture facilities that may be retrofitted relatively easily to produce these types of vaccines. Plasmid DNA and mRNA vaccines – non-viral vaccines that rely on bacterial fermentation – could use existing bacterial fermentation plants that are used to produce biotherapeutic proteins. Due to the large oxygen demands and heat removal requirements in prokaryotic fermentation, fermentation scales larger than 300L are not supported by single use technology.

Several of the different vaccine manufacturing processes are based on culturing live viruses (live attenuated vaccines, weakened vaccines, viral vector vaccines, viral particle vaccines and inactivated vaccines) where the initial process steps handle live viruses. These facilities will support some type of fermentation process for host cells that enable replication of the virus, as well as purification operations. The facility must be designed in compliance with biosafety containment requirements. These requirements are common design features in vaccine manufacturing facilities, but not in culture facilities which may not be easily retrofitted to meet these requirements.

Some vaccines have production steps, such as the manufacturing of an adjuvant or lipid particles used to deliver mRNA particles, that do not process pathogens but do require aseptic processing design and techniques. Lipid particles typically rely on solvents that are incompatible with single use technology and therefore must be produced in stainless steel equipment. The adjuvant or lipid particles cannot be sterile filtered and therefore the process equipment needs to be aseptic. Utilization of existing lipid particle facilities may be feasible, as the technology is somewhat standard and could be retrofitted easily to meet the vaccine process requirements.

mRNA vaccines require several manufacturing process steps that are not commonly used for vaccines. This includes bacterial fermentation to manufacture plasmid DNA. The plasmid DNA is used to make mRNA using an enzymatic process. The purification of the resulting mRNA is performed, according to size requirements, by precipitation and chromatography. Finally, the mRNA particle is embedded in a delivery vehicle such as lipid nanoparticles. The mRNA dosage is very small, reducing manufacturing scale. There exist few, if any, large-scale facilities that have all these manufacturing features and it is anticpated that new facilities will be required to produce large scale mRNA vaccines.

5. Manufacturing Capacity Requirements

5.1. Immunoglobulin

The global demand for human blood-derived immunoglobulin G (IgG) has nearly doubled in the past 8 years. This is due to the critical need to support clinical trials for novel drugs that address severe auto-immune, inflammatory, immuno-deficiency and other immuno-related disorders as well as the trend towards higher IgG treatment dosing for patients. Global and US demands for intravenous/ subcutaneous IgG, presented in Figure 1, suggest 2020 growth rates of 6 % will continue for the foreseeable future.

The four leading manufacturers, Grifols, CSL Behring, Takeda (formerly Shire) and Octapharma, supply 70 % of the global demand for Ig products. Plasma collections must continually expand to meet the projected Ig demand. A liter of donor blood plasma yields an average of 9 g of IgG. Current fractionation purification methods have improved greatly but still recover only about 4 g/L. To meet current global demand of 224 MM g/yr, at this yield, 56 MM L of blood plasma is required from at least 84 MM donations at 650 – 750 mL each. Based on 6% annual growth rate, this represents an increase of 4.8 MM blood donations over last year.

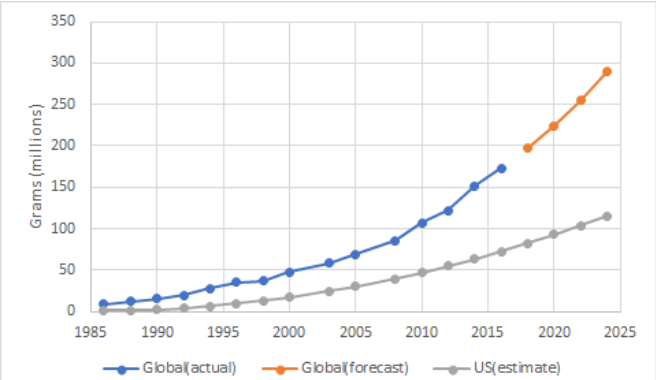

Figure 1: Global and U.S.A. IVIG/SCIG Demand, 1986-2018 and forecast figures up to 2024

Major plasma fractionators must invest in new production capacity to meet rising demand for Ig. A recently completed 3 MM L/yr plasma fractionation plant in Covington, Georgia cost $1+ billion and took 5+ years to build and acquire commercial production approvals. This implies greenfield large-scale facility production capacity costs $85/g Ig per year.

The Covid-19 pandemic creates an additional demand for Ig, to prevent infections for the highly exposed front-line medical and critical services workers. Assuming existing production facilities have no more than (an optimistic) 30 % spare capacity to serve these front-line workers, then no more than 67 MM grams of global fractionation capacity is available to serve pandemic needs in 2020. If enough patients recovered from Covid-19 infection and were willing to donate their plasma, this capacity would translate to no more than 1,900,000 workers (based on 35 g/treatment) that could acquire temporary passive immunity from the Covid-19 virus, with this immunity lasting several weeks or months. Booster treatments would be required thereafter to maintain effective immunity. For some perspective, the US alone has over 3,000,000 registered nurses and nearly 1,000,000 licensed physicians (10 – 15 million globally) within the 18,000,000 healthcare professionals. Clearly, the use of passive immunity provided from human plasma Ig will have little impact on the pandemic, other than keeping healthcare partially functional. The 5+ year timeframe needed to meaningfully expand capacity is too long-term to have any significant impact on the current crisis.

5.2. Small Molecule

There are several synthetically manufactured small molecule drugs that are approved for non-Covid-19 indications currently being screened and tested against Covid-19. As previously stated, the total number of severe cases of Covid-19 in 2020 and 2021 may reach 68 million. Some patients with severe cases may benefit from treatment with small molecule drugs.

As a test case, Remdesivir is a synthetically derived drug requiring administration by injection. The bulk drug substance is shipped to a sterile fill finish facility to complete the manufacturing process, making scale up of production capacity even more of a challenge, see Section 5.5. Gilead has targeted 1 million treatment courses by the end of 2020 and several million treatment courses in 2021[xvii]. Initial tests have indicated the need for up to 10-day treatment course per patient, indicating that the targeted production capacity is significantly below the potential need for this treatment.

In addition, like many anti-viral compounds, Remdesivir is of "moderate" complexity to synthesize. It requires up to 25 chemical steps and some 70 raw materials[xviii] (the original patented process). It currently takes some 9 months to fully manufacture a batch. It is possible synthesis can be further optimized, but the optimization is unlikely to be quick, and the synthesis will never be easy as the molecule has six chiral centers.

Gilead has signed licensing agreements with five generic pharmaceutical manufacturers based in India and Pakistan to further expand supply of Remdesivir. The agreements allow the companies to manufacture Remdesivir for distribution in low-income and lower-middle income countries, as well as several upper-middle and high income countries with significant obstacles to healthcare access. Under the licensing agreements, the companies have a right to receive a technology transfer of the Gilead manufacturing process for Remdesivir, enabling them to scale-up production more quickly. The licensees set their own price for the generic product. The licenses are royalty-free until the World Health Organization declares the end of the Public Health Emergency of International Concern regarding Covid-19, or until a pharmaceutical product other than Remdesivir or a vaccine is approved to treat or prevent Covid-19, whichever is earlier[xix].

This license agreement example may be applicable to other under patent, synthetically produced Covid-19 treatments, where the product and process may be available, but the production capacity is far below the demand.

5.3 Biologics – Existing Facilities

Potentially, the fastest and lowest cost option is to use existing biologics manufacturing facilities to meet the production requirements for treatments and vaccines. Larger pharmaceutical manufacturing companies will assess their internal manufacturing networks with the perspective of using spare capacity in existing facilities or to modify existing facilities to obtain extra production capacity. Large companies may also postpone production or even to displace non-critical

products in order to provide the necessary production capacity for Covid-19 related drugs.

A second option is to utilize Contract Manufacturing Organizations (CMO). Most of the announced SARS-CoV-2 vaccine development programs have involved some CMO network capacity. CMOs need to meet all pharmaceutical regulatory requirements, but the requirements contractually insisted upon by clients using the same process suites equipment can frequently be even more challenging. Compliance with client quality standards and control of product and viral cross contamination risks amplify the contractual complexity of bringing a new untested, and potentially ill-defined, process into a multi-product facility, and this process should not be underestimated.

Additionally, the tech transfer of a new product that is still under development and may undergo developmental changes to both the process and analytical methods, is difficult within a company. This becomes even more fraught when the transfer is to a CMO facility, with its own inherent corporate quality standards and culture.

The available manufacturing capacity within CMOs is also of concern. Very few new, mid-sized CMO facilities with production fermenter capacities of 1,000L or greater have come online over the past five years in the United States and Europe[xx]. Recently, major CMOs have preferred mergers and acquisitions over internal expansion. Many new CMOs have started up, but they are nearly all smaller specialist companies, often supporting cell and gene therapy manufacturing (volumes < 100L). Not all the announced Covid-19 programs will actually progress to requiring manufacturing capacity. While there is a limited amount of spare capacity within the CMO networks, it is possible that there will be more manufacturing programs seeking, or relying on, CMO manufacturing capacity than actually exists.

A third option to meet production requirements is to form partnerships, create alliances and forge licensing arrangements. This can be particularly useful for producing at an affordable cost in, and for, developing countries. In the biologics space, the collaboration between Sanofi and GSK[xxi] to produce a Covid-19 vaccine and its associated adjuvant, is a great example of maximizing the specialties and capabilities of each company. Partnering is a great option for smaller pharmaceutical companies that have neither the manufacturing capacity nor the capital to either use a CMO or build the facilities themselves. Oxford University has partnering agreements with Astra Zeneca as well as the aforementioned Serum Institute of India to produce their vaccine candidate for different markets. However, as with CMOs, tech transfer, quality standards and corporate culture all pose problems for partnering/licensing agreements.

Considering the potential volumes required, choosing to pursue more than one of these options could put a company in an advantageous position. For example, Johnson and Johnson indicated in their announcement[xxii] that they are planning on using some of their spare internal capacity, are partnering with a CMO for additional capacity and in addition are planning on building new internal manufacturing capacity.

Expanding or retrofitting existing licensed manufacturing facilities is an appropriate mid-term solution to increase production capacities. Modification of facilities requires a thorough process-fit gap-analysis. The requirements for a manufacturing process are dependent on the manufacturing approach, the cell line, and the chosen vaccine technology platform. If the vaccine technology chosen requires use and handling of the novel SARS-CoV-2 virus in a live format, significant modifications to the existing containment practices may be necessary. It is therefore likely that existing equipment and facilities may need to be modified, or new equipment ordered. Some of the more complex large systems fabricated in stainless steel have long lead times. Application of smaller scale single use solutions may prove beneficial to accelerating the timeline.

Figure 2: A large-scale biologics manufacturing suite (top), picture from DPR.com. Biologics manufacturing equipment under construction off site (bottom), picture from Zeta.com

Figure 2 captures two of the difficulties to retrofit/repurposing - a typical active large-scale biologics clean room, and a highly complex manufacturing facility for

new equipment. Both the complexity of working within an existing manufacturing space, and building and fitting new equipment into these spaces should not be under-estimated.

Separately, each facility will require careful evaluation to identify all bottlenecks that may be limiting capacity. Common bottlenecks can include, but are not limited to, clean utilities generation/distribution (e.g. clean steam, purified water), chilled water, liquid waste neutralization, raw material staging/logistics, media/buffer preparation turnaround, variable manual or inefficient automated cleaning of equipment and small parts, autoclave or depyrogenation capacities and solid waste handling. Opportunities identified during the evaluation will need to be ranked with consideration for the realizable capacity increase versus cost and time to implement.

Vaccine manufacturing facilities may require biosafety containment when processing a pathogen. The SARS-CoV-2 live virus is classified as a BioSafety Level (BSL) 3 organism. Some viruses used for viral vectors only require BSL-2 containment intended to address agents associated with human disease and moderate risk to personnel and environment. The first vaccine proven to be safe and effective might require the use of a live organism, which would require a facility capable of handling a BSL-3 process, one that can cause serious or potentially lethal disease through inhalation. The use of a powered air purifying respirator (PAPR) in combination with a class II biological safety cabinet (BSC) required for BSL-3 environments would need extensive design and operational considerations.

Figure 3: A BSL-3 laboratories/facilities, gowning and containment, credit CDC PHIL, #23209

Upgrading an existing facility from BSL-1 to BSL-2 or BSL-3 requires improved containment. This typically requires closed processing, a higher level of personal protection equipment (PPE), ready access to handwash sinks and eyewashes, restricted personnel access during operations, and self-closing doors. All waste streams require double-bagging and/or inactivation such as a bio-waste inactivation system, decontamination autoclaves or other approved equivalent. Open process manipulations are expected to be performed in an appropriate biosafety cabinet or laminar flow hood. Continuous unidirectional airflow in the processing suite and prohibiting the use of any recirculated air in the room is required. Implementing these modifications may, in some cases, prove to have too much impact on other production activities.

To start producing a Covid-19 drug, the manufacturing process developed in laboratories and pilot plants will need to be tech transferred to the existing manufacturing facility. This is complex and time consuming, especially for a product that is still in early clinical trials and may be subject to changes.

Facility, equipment and process changes due to retrofitting and debottlenecking need to be commissioned and qualified prior to manufacturing according to cGMP requirements. When following the traditional commissioning and qualification models, this can be time consuming, postponing the availability of relief from a treatment or vaccine. Implementing risk-based qualification in accordance with the ASTM-E2500 method can significantly shorten timelines. This method frontloads assessments to streamline the testing activities and focuses on testing the critical elements. Quality audits and design collaborations with the equipment vendors and construction firms can reduce errors and rework. With a proper change control system, test results can be leveraged to avoid repetition. To implement this approach successfully, it is necessary to develop and agree on the strategic approaches used during commissioning and qualification at the start of the project. This approach is fully accepted by regulatory agencies, but the industry has been slow to embrace all aspects and streamline activities. This is often because of the reluctance of quality departments or because planning for commissioning and qualification is started after the design has been developed and it is therefore more challenging to fully realize all benefits of the ASTM-E2500 method. However, the urgency of the current scenario, and potential gains in expediency, may entice pharmaceutical manufacturers to take the steps to fully embrace this methodology.

The introduction of a new product to an existing facility requires the reduction of current and potential modes of cross-contamination to pre-defined, acceptable levels. For multi-product facilities, this is a routine process, however dedicated facilities, or dedicated specialty equipment, within a multi-product facility may require significant engineering changes to mitigate cross-contamination risks. Specifically, dedicated equipment is often employed in a multi-product facility because the path to preventing cross-contamination is costly or prohibitively onerous.

Many current vaccine facilities are product dedicated, and with good reason. Biotherapeutic manufacturing facilities have many similarities with vaccine manufacturing processes. However, using them to manufacture vaccines has substantial hurdles. Facilities that want to produce several vaccines must address cross contamination risks, which are more challenging than for biotherapeutic multiproduct facilities.

Firstly, vaccines have a very high potency, therefore the allowable residue carry over between vaccine manufacturing campaigns is usually very low. Vaccines are typically significantly more potent then biotherapeutics. The larger dose of biotherapeutics will require that the carry-over of residual vaccines is reduced even further. This requires high cleaning standards and most likely the use of product dedicated equipment and single use equipment.

Secondly, vaccines carry the risk of viral contamination of a manufacturing facility and equipment that were not originally designed to address this level of risk. The threat of viral cross contamination must be addressed, which may result in facility modifications to provide additional viral segregation and inactivation.

Additional levels of product and viral inactivation may require chemical and thermal treatment of the production equipment. These risks may prevent a facility that has been used to manufacture a vaccine from being switched back to biotherapeutics.

5.4 Biologics – New Facilities

There are many existing biologics manufacturing facilities already installed throughout the world. Using the existing platform technologies for any required biologic-based treatments within the existing biologic manufacturing network may cover the manufacturing capacity requirements without the construction of new capacity. But it is likely that there is insufficient existing vaccine manufacturing capacity available to meet the expected demand for a Covid-19 vaccine, and new biologics facilities may also be required for treatments.

Typically, new biological facilities have a timeline of several years from design to startup. With the expedited clinical trials for Covid-19 drugs, any new facilities need to be constructed and started up in record times of one year or less. There are several strategies that can be used to reduce the overall design, construction, and startup time.

The first step involves the design and construction of a facility prior to gaining full knowledge of which vaccine will be successful. Therefore, it is important to develop and construct a flexible, standard design that can be re-aligned rapidly.

Biologic manufacturing facilities that will be designed and built to produce Covid-19 drugs can be characterized in three families: non-viral (treatments, plasmid, subunit vaccines, recombinant and viral particles), viral (live, attenuated virus, or viral vectors), or mRNA. The three families will require different types of core manufacturing capabilities combined with similar utilities and infrastructure wrapped around the core. The focus of the viral plant will be the cell culture process, viral infection and containment of the virus. The focus of the non-viral plant will be on standard monoclonal antibody manufacturing processes. mRNA plants will focus on cutting edge plasmid technology and enzymatic chemistry.

With all of these technologies, the goal will be to build the new facilities in the fastest possible manner. Optimizing the technology and the facility design will take more time than is available. Construction will need to start before the process for the new vaccine has been fully developed, requiring flexibility in the design to accommodate rapid modification to support process changes. Disruptive, fast and/or low-cost construction techniques for elements that are typically long-lead must be explored. These elements include the building, fermenters, and centrifuges. Standard proven platforms should be used for high-risk or essential elements of equipment, and it will be important to use the standard design platforms (traditional attenuated viral and mAbs) to capture the extensive existing industry understanding. This will result in a “good enough” manufacturing facility.

Figure 4: A typical single use mAb facility, picture by WuXi Biologics

The Covid-19 pandemic has caused severe dislocations in the pharmaceutical supply chain. Additional vaccine manufacturing capacity will have to be geographically diversely distributed to address both supply chain and political risk. Using modular technology for the standard design will support replication around the world, particularly in countries where expertise and infrastructure are lacking. Modular technology can also lessen the impact of social distancing on the on-site construction techniques. This is already being seen on existing construction projects.

Creating a strong partnership between the pharmaceutical manufacturer and the team responsible for design, construction, commissioning, and qualification at the start of the project will reduce valuable time for quotation and learning curve between the different project stages. The use of an existing shell space will also save significant time in design, permitting and construction of the exterior. The clean rooms can be constructed using modular clean room technology, allowing rapid changes at a later stage. Single use technology should be considered to shorten the equipment delivery time, as well as commissioning and qualification time. Finally, the use of risk-based qualification strategies will be required to meet the aggressive schedule.

mRNA vaccine production facilities have their own challenges. As this is a new type of vaccine technology and process, there are no existing commercial mRNA facilities that can be utilized to offer experience or guidance to any Covid-19 specific efforts. The process requires facilities that can handle plasmid fermentation, enzymatic cleavage and Lipid Nano Particle (LNP) manufacturing. The first two steps are performed on a relatively small scale and new facilities can be rapidly constructed using existing technologies. Utilization of existing lipid particle facilities may be feasible, as the technology is somewhat standard and could be retrofitted to meet the vaccine process requirements. But many of the large-scale LNP manufacturing facilities are used to produce other (often critical) drugs and may not have extra available capacity. Fast construction of new LNP manufacturing facilities may prove to be a challenge, as the LNP process typically requires solvents, which is problematic for existing single use technology. LNP large-scale manufacturing equipment is typically fabricated from stainless steel and requires clean-in-place and thermal sterilization, as the lipid particles cannot be sterile filtered, thereby requiring aseptic processing. Additionally, some of the projected LNP formulations will require a -80 °C cold chain. While not impossible, a -80 °C cold chain, increases the complexity of the project and may be very difficult in large parts of the world. While it is likely that future development could eliminate this requirement, that development will take precious time.

5.5 Sterile Fill-Finish

Often referred to as fill-finish facilities, the final formulation, filling, inspection and packaging of the bulk drug vaccine is typically performed in a different manufacturing facility to where the bulk drug substance is produced. Sterile fill-finish drug products, including vaccines, biologics and some of the synthetic treatments, all use very similar equipment and facilities. The product is formulated to its final composition, before it is sterile-filtered and filled in a vial (Figure 5), a syringe or a Compact Prefilled Auto Disable (CPAD) device. The container is then closed, inspected, labeled and packaged.

Most Covid-19 vaccines under development will be a parenteral (injectable) solution, typically filled in a glass vial or prefilled syringe. New technology is also being explored, such as the potential for micro-array patches where the vaccine may be stable at ambient temperature and can be administered via an adhesive patch placed temporarily on the skin. This technology will need to pass through the clinical trial and approval process. Additionally, the technology requires a different manufacturing plant and it is estimated that once manufacturing facility plans are in place, the timeframe from breaking ground to a fully validated, operational pilot plant will be 2 to 3 years.

Figure 5: A typical vial fill line

Orally administered vaccines are also being developed. Stabilitech, a UK-based firm, is working on an oral vaccine that is filled in an ampule[xxiii]. Vaxart, a South San Francisco based company, is developing an oral vaccine that is administered by tablet[xxiv]. These oral vaccines do not require refrigeration, are easy to administer and can provide a low-cost solution. But parenteral vaccines are the primary target and this article will focus on facilities that support that format.

The global fill-finish manufacturing market is predicted by Markets and Markets[xxv] to expand at a CAGR of 8.6 % from $2.96 billion in 2017 to $4.47 billion in 2022. Europe is expected to account for the largest share of the market, while Asia Pacific will experience the most rapid growth. Due to special expertise and the challenges associated with aseptic fill-finish operations today, many biopharmaceutical companies are relying on CMOs to manage this important step. Biomanufacturers have been shown to outsource over 30% of their fill-finish operations. Over 100 companies are currently providing fill-finish services for prefilled syringes, although stricter regulatory oversight has led some contract manufacturers to exit the market.

Construction of new fill-finish facilities is typically a costly and lengthy process. Complex fill-finish lines with vial washers, depyrogenation tunnels, and integration into isolators may have lead times close to 2 years. Automated inspection machines that can handle large volumes also have extensive lead times. Therefore, new facilities are not likely to be providing additional near-term capacity for the Covid-19 vaccine production demands, and existing fill-finish facilities will have to be utilized.

Most fill-finish operations use very similar facilities and equipment and are typically designed for multi-product operations. The challenges with using existing fill-finish operations are capacity, suitability and flexibility for the new product.

Many existing fill-finish facilities have long production pipelines; changing production planning may impact the output of other products that were scheduled to be produced. Another consideration is whether the existing fill-finish facility can support the required production capacity, possibly in the order of one billion doses per year. Since much of the fill-finish operations are handled by CMOs, there may be flexibility to rapidly provide some additional capacity for novel Covid-19 vaccines. In addition, the industry may be required to form new alliances to share fill-finish capacity.

The suitability and flexibility challenges to utilizing existing fill-finish operations come down to the fill-finish individual dose-fill volume, the delivery format, cross-contamination issues, biosafety requirements and the ability for the facility to be retrofitted as needed.

The dose-fill volume is often determined by the fill equipment (e.g. vial washer, depyrogenation oven, filler) limits, and automated inspection unit capacity. This equipment is limited in scalability; therefore, the facilities tend to have a limited individual dose-fill volume range.

Existing fill-finish lines have limited flexibility regarding the format in which the vaccine can be filled. Equipment is designed to fill either vials or pre-filled syringes and cannot be modified for a different format, even though the filling equipment can be adjusted for the size of the vial or syringe. Vials are made from glass, a proven technology, however, significant supply chain issues exist, and shortages have been reported since 2015. Recently, the medical glass industry was beginning to catch up with the increased demand, but Covid-19 vaccines will create additional pressure. Even if the vaccine is filled into vials containing 10 doses hundreds of millions of vials are required. Jansen Pharmaceuticals, a division of Johnson and Johnson, has already preordered 250 million vials to minimize this risk[xxvi]. Pre-filled syringes and CPADs may be an alternative, but with a higher cost of goods[xxvii].

The risk of cross-contamination is also present when considering the use of existing fill-finish facilities. Many existing fill-finish lines use stainless steel process contact surfaces. In these cases, cleaning validation is required to demonstrate robustness and effectiveness of cleaning prior to product change over to prevent cross-contamination of the other product filled with the same process equipment. Vaccines are, in the main, more potent than and require smaller therapeutic doses than most other biotherapeutic drugs, making cross-contamination a valid concern. It is therefore likely that only fill-finish operations that are currently tailored to other vaccines will be suitable for the Covid-19 vaccine.

To protect manufacturing staff, and the environment, from the dangers of the biological pathogen, biosafety requirements will most likely have to be developed for a novel Covid-19 vaccine. It is expected that many of the novel Covid-19 vaccines may require BSL-3 facilities and controls. Facilities not designed for BSL-2 operations can typically be retrofitted to meet these requirements. However, it is not feasible to retrofit an existing filling operation to one contained by isolators, and a BSL-3 retrofit in a BSL-1 facility will be problematic. Many existing vaccine filling operations are designed for BSL-2 level operations and therefore may be suitable for the new Covid-19 vaccine production.

6. Summary and Conclusions

While the rate at which the disease will spread in the next year is unknown, it is safe to say that millions of people may need some treatment as soon as possible. Several treatments are already in phase 3 clinical trials and may soon be approved. We may require large quantities of these pharmaceuticals in a very short amount of time. But, the need for treatments may subside if efficacious vaccines are found and approved. Ultimately, vaccines may be the only type of drug capable of halting the pandemic and providing the world with relief. This would require sufficient vaccinations for approximately 5 billion people. As the vaccines are still being developed, the dosage requirements and the need for boosters is unclear. Nor is it clear how fast this virus will mutate, but we may need different vaccines, after some time, in order to retain immunity. All in all, the manufacturing quantities that will be required are enormous.

Many companies are working on treatment and vaccines but finding the manufacturing capacity to meet the need for these drugs will be a problem of a different nature. It is not likely that new facilities will be built to meet this temporary high demand. Treatments may be produced rapidly by retrofitting and debottlenecking existing manufacturing facilities, or with partnerships between different

organizations. The production requirements for vaccines are even more substantial, and potentially have a longer-term need. There may be some additional time to work on the vaccine manufacturing challenges as the approval of new vaccines will take longer. To meet the vaccine manufacturing requirements, the industry is looking at utilizing existing facilities, partnerships, and CMOs. But there will likely be a need to rapidly construct new flexible facilities that can adapt to the exact vaccine(s) which proves successful. Standard designs using modular technology can expedite construction timelines and overcome the particular difficulties of building these complex facilities in developing parts of the world.

7. What More Can We Do?

In the next article, we will review the industry, governmental and NGO initiatives dedicated to developing treatments and vaccines for Covid-19. Positive advancements in drug development and manufacture will come out of the pandemic that will further health care for other diseases. But who will get access to successful treatments and vaccines?

We will discuss additional measures that may help with the Covid-19 pandemic, but also may better prepare us for the next pandemic. Covid-19 is a reminder that infectious diseases are a global problem requiring global solutions.

We will examine ways in which the pharmaceutical industry can reduce the time required to bring new manufacturing capacity on-line. We will look at the assumptions we make with regard to design, procurement, construction and qualification of manufacturing facilities. Since this review suggests new manufacturing capacities will be required world-wide to meet the enormous requirements of this pandemic, the corresponding requirement will be to develop new ways of bringing that capacity on-line at an unprecedented speed.

About Hyde Engineering + Consulting

Hyde Engineering + Consulting is a global design and consulting organization providing process system design, commissioning and validation, FDA compliance, and state-of-the-art cleaning technologies to pharmaceutical, bioprocess and other regulated process industries.

Global capabilities and offices throughout the United States, Europe and Asia gives Hyde clients the convenience of a single worldwide partner. Our staff of over 200 professionals are dedicated to understanding client needs and exceeding their expectations.

Regardless of the size of the facility or complexity of the project, Hyde provides peace of mind through global expertise.

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