Syngene

Putting Science to Work

Manufacturing vaccines during COVID-19

CMOs/CDMOs to the rescue

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VIEW POINT

Introduction

The Healthcare sector was never in greater focus than in 2020. With the pandemic continuing unabated, the world looked to Science and the scientific community for deliverance. And Science did not disappoint. In less than a year of the pandemic, thanks to concerted global efforts, more than 150 vaccine candidates became available as a possible cure for COVID-19.

While 2020 was all about discovering a vaccine, 2021 is going to be about how to take the vaccines to market in the shortest possible time. With more than 2.6 million deaths worldwide (figures as on 9 March, 2021) and counting, the need for speed cannot underscored.

However, to decipher the manufacturing challenge, one needs to understand what goes behind producing a vaccine — raw materials, technology, and a complex manufacturing process. And finally, how and why Contract Manufacturing Organizations (CMOs)/ Contract Development and Manufacturing Organizations (CDMOs) are better positioned to bridge the gap between vaccine demand and supply, safely and at speed.

Types of vaccines

Vaccines are generally classified as follows:

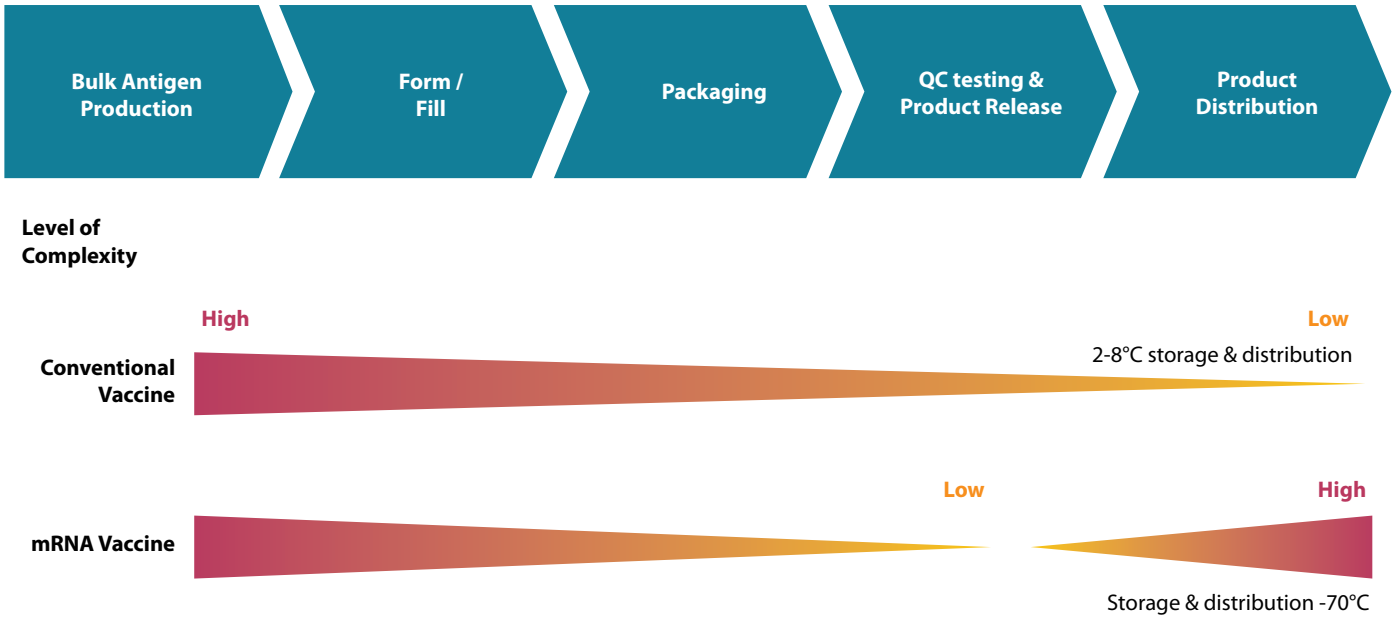
COVID-19 vaccines being developed, currently, are based on these platforms.

Various Expression Systems and Hosts are used to produce the vaccine candidate. As shown in the image below, we can consider no single expression system an overall "best option" since each one has certain advantages and disadvantages. Also, not all expression systems can be used to produce all antigens. Hence, the options available also depend on the vaccine to be manufactured.

	Low → High			
Speed	Mammalian	BEVS/Insect cell	Yeast	Bacteria
Cost	Bacteria	Yeast	BEVS / Insect cell	Mammalian
Typical yield	Mammalian	BEVS / Insect cell	Bacteria	Yeast
Post-translational modification	Bacteria	Yeast	BEVS / Insect cell	Mammalian
Regulatory approval	BEVS / Insect cell	Yeast	Bacteria	Mammalian

Vaccine manufacturing process

The key steps in manufacturing vaccines are as follows:



Challenges in manufacturing vaccines

While COVID-19 vaccines surpassed all expectations by becoming available to the general population in less than a year, this is an exception rather than the norm. A typical vaccine usually takes 10 to 12 years to reach the market after discovery efforts begin. With most pharma and biotech companies using conventional facilities for manufacturing vaccines, this leads to further delays.

Limitations of conventional facilities

Convention facilities have limited flexibility and are capacity constrained. Hence, they cannot handle a sudden spike in demand -- as necessitated during a pandemic or an outbreak such as COVID-19. Commercial manufacturing facilities are also dedicated to a specific vaccine product, and do not have the flexibility to switch to producing large volumes of a new vaccine. This is especially challenging because interrupting vaccine production can lead to the failure of national immunization programs that deliver mandatory vaccines for Expanded Programme on Immunization (EPI). High upfront investment during product development is also deemed risky, given the uncertainty of Phase-III outcomes and demand, post-launch.

Cost implications of building new capacities

For biotech and pharma companies to build new capacities, it would be a risky proposition, given the huge capital expenditure involved.

The cost of setting up a new vaccine manufacturing facility with supporting functions and having a capacity for 100 million doses is estimated to be around $60-80 million. Supporting operations would include Utilities, Quality control (QC), Quality Assurance (QA), Warehouse, and effluent treatment systems for environment clearance. Further, it would take approximately 3-5 years for the facility to be fully operational.

Some other challenges include:

- High-quality equipment with automation controls that need time and coordination for interfacing with existing systems
- Need to set up end-to-end sterile processes requiring high integrity of equipment, utilities, and facility with vital environmental monitoring programs
- Significant levels of checks and control points to preserve compliance
- High level of qualifications to ensure compliance and sustainability
- Intense and time-consuming testing for utilities and facility validations
- Inability to perform terminal sterilization due to the sensitive nature of vaccines

It is also true that the cost of setting up a manufacturing facility for vaccines is 2-3 times more than the cost of setting up a facility for small molecules. Even in terms of operating expenditure, the cost of manufacturing vaccines is higher by 1.5 to 2 times as compared to small molecules.

Regulatory challenges

Vaccines are one of the most regulated materials in the pharma and biotech space. Historically, vaccines have been subjected to limited characterization, and hence robust regulation and oversight are necessary to ensure vaccines are safe.

Even after a Biopharma company has gained approval for the biological product application, post-license monitoring must confirm that the vaccine usage is consistent with proven clinical studies, and the finalized, approved manufacturing and release process, has been maintained.

License amendments are also required to confirm that any change to the intended use of the vaccine in different populations or/and changes to the manufacturing process (seeds, raw material sources, process steps, release steps, equipment, facilities, etc.) do not adversely affect the product purity, safety or effectiveness.

Distribution challenges

Distribution challenges involve logistic and cold chain management as vaccines are very sensitive. A reliable infrastructure across the supply chain is needed to maintain product potency and safety, until administered. Different vaccines also have different sensitivities. Some examples of sensitivity include:

- Heat-sensitive vaccines like oral Polio vaccine (OPV), Measles, Mumps, and Rubella (MMR), HPV and Influenza
- Light-sensitive vaccines like Bacillus Calmette-Guerin (BCG) for tuberculosis & MMR
- Live vaccine (Bacterial or viral) are prone to potency loss through exposure to higher temperatures
- Non-live vaccines are more stable in higher temperatures but often sensitive to freezing because of adjuvant.

The finished product of vaccines must also be stored at 2-8°C while others require -80°C (which may be challenging to maintain during distribution). This is the case even with COVID-19 vaccines which have received approvals, recently. It is seen that different vaccines have different storage requirements, which pose a huge distribution challenge.

Advantage CMOs/CDMOs

Easing capacity constraints

In such a scenario, using CMOs/CDMOs to take on vaccine manufacturing provides significant risk mitigation. For starters, they could ease capacity constraints, and help in responding more quickly to changes in demand. For example, today, various vaccine approaches being taken to address COVID-19, rely on r-proteins, viral vectors, or mRNA. Many CDMOs already have the expertise in this area to produce first-generation vaccines, at speed.

Accelerating regulatory approvals

Vaccine manufacturers can also accelerate regulatory approvals if regulators have previously authorized similar products before.

For example, several platform technologies being used to produce COVID-19 candidate vaccines are relatively untested. The resulting vaccines' modular nature could mean, that regulatory approval can be expedited, as these technologies become more common place.

Flexible Facilities

Most CMOs/CDMOs also use flexible facilities with single-use disposables for manufacturing, which has several advantages. This is as opposed to reusable systems used by traditional Biopharma companies who usually have conventional facilities. The conventional facilities use stainless steel for upstream and downstream activities which have several disadvantages that need to be addressed (Refer Tables 1, 2, and 3 below).

Table 1: Facility with Single-Use Platform Vs. Facility with Conventional Platform

Facility with Single-Use Platform	Facility with Conventional Platform
Small plant footprint, Flexible infrastructure	Large area for plant footprint, Fixed infrastructure
Cost of Goods (COGS): Higher consumables use, Low maintenance cost	Cost of goods (COGS): Reusable equipment, High maintenance cost
Production volumes limited to 2 KL	Can handle high volumes of 10 KL and above
Ballroom Concept: can handle multiple process activity in a single room	Dedicated Process areas for process activities
Minimum utility consumption as equipment cleaning is not involved	High utilization of Utilities, as CIP/SIP is involved
Quick changeover, hence short process cycle time and a more significant number of batches possible, annually	Slow change over time as CIP/SIP is required post every batch, hence longer process cycle time.
Possible to handle multi-products in a single process room	Dedicated to a single product
Low CAPEX, but higher OPEX due to consumables consumption	High CAPEX, but low OPEX
Lower cleanroom classification acceptable to carry out process activities, hence lower HVAC cost	Requires higher classification, Higher HVAC cost

Table 2: Upstream Process — Single-use system Vs. stainless steel system

Flexible Single-Use	Reusable Stainless Steel
Equipment with a smaller footprint – hence smaller facility can handle large batch sizes	Equipment with large footprint – facility with larger area required
All flexible connections – easy to dismantle and reassemble bioreactors	Rigid pipe connection – fixed connections
Single-use mixers and holders –No CIP/SIP. Hence, it reduces process cycle time and enhances product output	SS mixers and holder for handling process volumes – CIP/SIP required, hence increased cycle time
Leachables and extractables of single-use bags	CIP process to be-validated for the elimination of contamination
Minimal risk of cross-contamination	Chances of cross-contamination between batches
Mobile equipment – easy for process volume transfers from one process area to another	Fixed equipment – need transfer panel for fluid process transfer
No CIP/ SIP -- Less consumption of utilities	CIP/ SIP required – more utilization of utilities in equipment cleaning
Faster time-to-market	Longer duration for product release to market

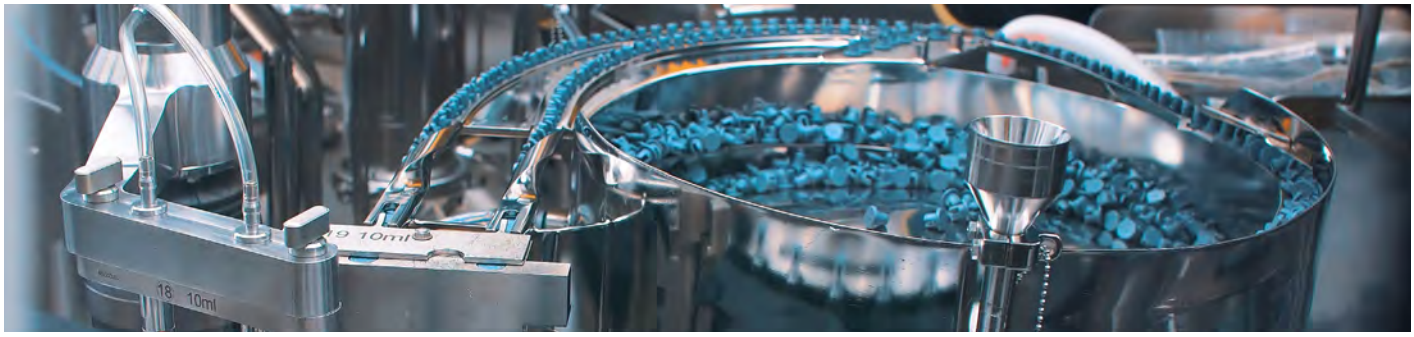


Table 3: Downstream Process — Single-use system Vs. Stainless steel system

Flexible Single-Use	Reusable Stainless Steel
Half the process cycle time as compared to a reusable system	Longer cycle time
Chromatography: Prepacked columns, reduced/ minimal risk of bioburden	Chromatography: Manual column packing increases the risk of bioburden
Single-use flow path — Easy switch-over between batches and products	Reusable flow path — longer change over time with CIP/ SIP of the flow path
Less waste generation	A large volume of waste generation due to CIP
Minimal risk of cross-contamination	Chances of cross-contamination between batches
The increased operational cost of consumables	Reduced process cost
Easy scale up from PD to clinical scale	The limited scope of scale-up
Flexibility to handle - production volume of different scales	Limited to handle a small range of process volume

Distribution capability

CMOs/CDMOs are better equipped from a distribution perspective as well. They have access to well-organized, cold chain transport systems comprising Envirotainer, cold box, and refrigerated reefer for temperature-sensitive products. These ensure, product safety and efficacy of the vaccines are maintained until delivery.

Syngene's capability and capacity in vaccine manufacturing

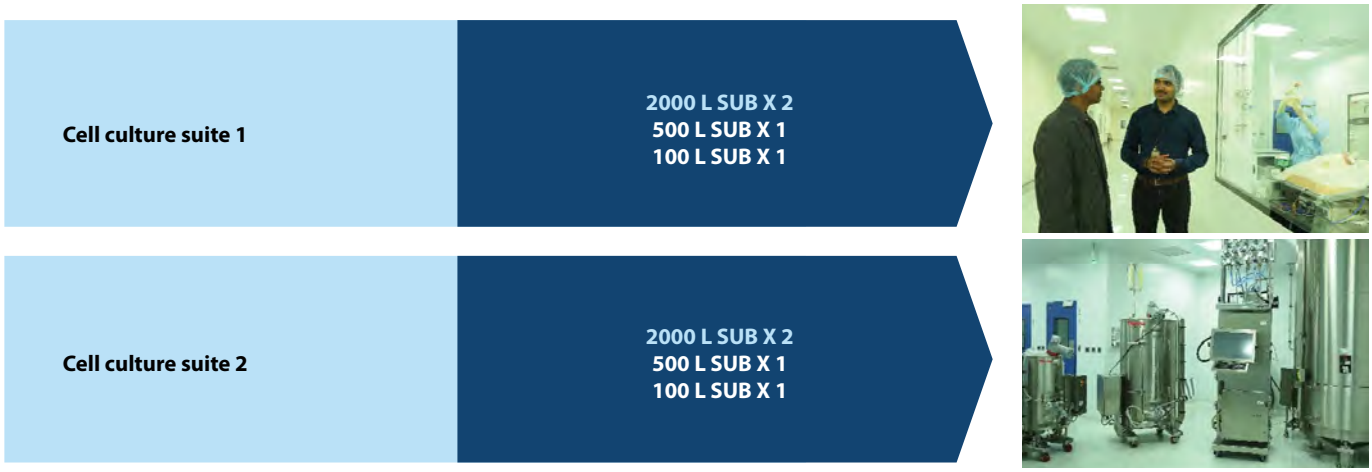
CMOs/CDMOs like Syngene can offer end-to-end services across the manufacturing value chain. Our cGMP-complaint facilities are equipped with flexible, single-use systems for both upstream and downstream activities, and provide advantages of space, time, cost, and compliance.

Mammalian manufacturing:

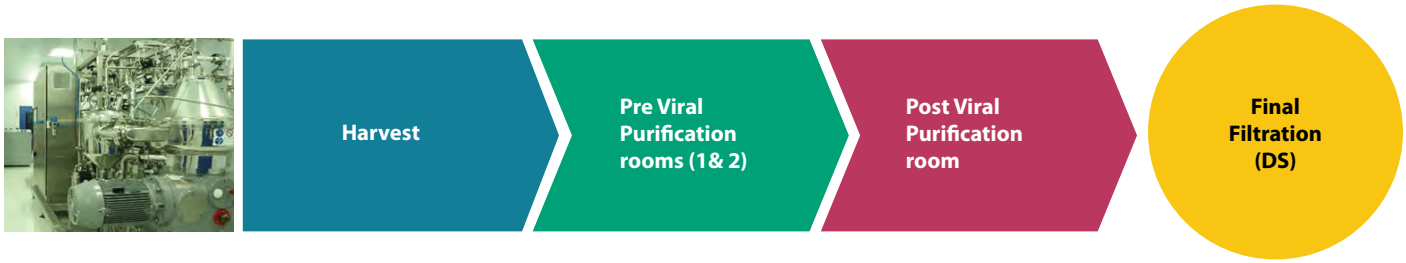
For its disposable-based mammalian facility for clinical and commercial manufacturing supplies, Syngene has 4 x 2,000L Single-Use bioreactors to support cell expansion 100 →500 →2,000L. It has 3 x 2KL bioreactors currently in operation. While two Upstream suites allow parallel processes, Harvest is by centrifuge or depth filtration, and downstream comes with post-viral segregation.

Upstream manufacturing:

Our Upstream capabilities include two suites (from Inoculum to Production reactors), 3 x 2KL



Harvest is by Continuous centrifuge (up to 2000 LPH flow rate) and/or Depth Filtration (up-to 44 sqm area).



Our Downstream capabilities include:

- Pre-viral (two rooms – with all chromatography steps, UFDF, Viral filtration)
- Post viral (one room – UFDF and final filtration – closed operation),
- Can handle products with 4 chromatography steps – Flow rate up to 2000LPH
- Column size > 800mm (depends process and operating conditions), currently till 600mm

Microbial manufacturing:

Our cGMP facility for microbial manufacturing can produce recombinant proteins from bacteria and yeast cell with intracellular or secreted expression.

Critical equipment includes 200L (SS) and 500L (SS) fermenters, Continuous centrifuge, Cell homogenizer, Chromatography systems and TFF systems.

The facility can take up manufacturing scale of 500L (SS) fermentation upstream, continuous centrifuge of 200LPH, Homogenization of 300LPH, and downstream process using 1000L refolding single-use system. It has 600 to 2000LPH Chromatography system with associated columns up to 60cm, 10 sqm tangential flow filtration, and final filtration of drug substances.

Syngene's Capability and Capacity in newer vaccine platforms

We have the capability and capacity to produce 5–200 million doses of equivalent drug substance across Protein Sub-units, r-BEVS, mRNA, and Viral Vector vaccine platforms. These are the new approaches currently being used for manufacturing vaccines for COVID-19. The manufacturing facilities comply with the biosafety requirement of BSL-1 and BSL-2, which provide a broader opportunity in manufacturing vaccines across different platforms.

Conclusion

COVID-19 has taught the world the value of scientific collaboration in discovering, producing, and distributing a vaccine, quickly. Technology has also played a significant role, especially when it comes to mRNA vaccines being developed by Moderna and Pfizer. These could well lead the way in combatting other deadly viruses in the future.

However, to avoid high rate of fatalities as with COVID-19, manufacturing processes and technologies must evolve. Speed of response from threat identification, testing protocol implementation to vaccine deployment, needs to increase. Flexibility in manufacturing a wide range of vaccines should also be available.

Currently, CMO/CDMOs like Syngene are uniquely positioned to meet this challenge. Years of collaborating with clients has helped them become knowledge centers in themselves, besides being technologically ready to take up new challenges.

Biotech and pharma companies need to take advantage of CMOs/CDMOs' superior knowledge and expertise, and partner with them for manufacturing vaccines in the shortest possible time.

About the authors

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Mahesh is a biotechnology and Biologics leader with over 25 years of experience. He has been associated with companies such as Amgen, Sanofi, Celera Genomics, Molecular Probes and Monsanto in the past. He is a member of CII's National Committee on Biotechnology, the Expert committee at United States Pharmacopeia, and the Indian Pharmacopeial Commission. Mahesh holds a Ph.D. in Medicinal Chemistry from the University of Utah (USA) and a B.Pharma from the University of Mumbai.

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Satish Kumar Manjunatha has over 16 years of experience in the Biopharma industry. He has been associated with Indian Immunologics Limited, Cadilapharmaceuticals and Sanofi in the past. He has experience working with different vaccine platforms such as bacterial, yeast and viral vaccines related to process development, manufacturing of investigational products and commercial manufacturing. He has a Post-graduate degree in Biotechnology from Bharathidasan University.

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