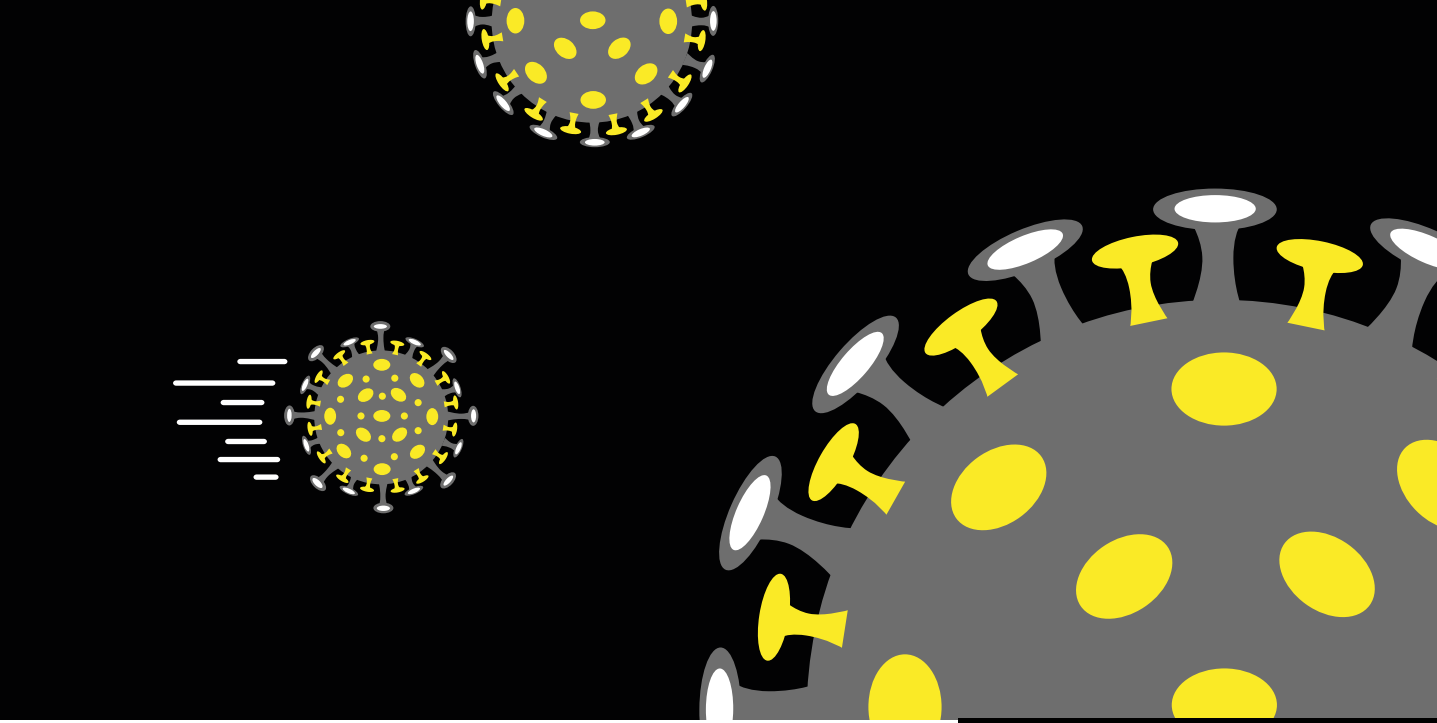

Success at Speed

Digging into Accelerated Vaccine Development

Simplifying Progress

SARTORIUS

Introduction

There are many lessons to learn from the COVID-19 pandemic regarding preparedness for a future pandemic or virus outbreak. Amelie Boulais and Piergiuseppe Nestola, Vaccine experts from Sartorius, documented each step in the journey to accelerate vaccine development for COVID-19 in a series of articles. The articles have been compiled together in this eBook.

At the start of any virus outbreak or pandemic, the imperative is to accelerate vaccine development without sacrificing safety or efficacy. In other words, how to create 'success at speed.' Vaccine developers and manufacturers grapple with numerous questions and uncertainties around expedited development, such as meeting regulatory requirements, vaccine efficacy, and production capacities.

This leads to the more fundamental decision to select the best-suited strategy for vaccine development, i.e., the selection of a vaccine modality.

In this eBook, we discuss how the chosen platform has implications on time taken for development. As predicted in the first few articles, the vaccines that have emerged as front runners to combat COVID-19 are based on the viral vector or mRNA platforms.

It is easy to assume that vaccine research and development is followed by vaccine manufacturing in neat sequential order. However, the real challenge in accelerating bringing a vaccine to market is that scientists have to start with the end in mind.

The complexities of the vaccine manufacturing process had to be considered at the early development stage and during platform adoption. The next dilemma is how to rapidly scale up from small scale to full commercial scale to supply the billions of doses needed while still balancing costs and safety. The final stage in successfully combatting a pandemic is distribution, accessibility, affordability, and all the logistical challenges associated with those problems.

Many questions remain to be solved before the world is sufficiently prepared to handle such an outbreak in the future. This ebook summarizes some of the key learnings for the biopharmaceutical industry through the pandemic and suggests a course to improve preparedness for the future.

About the Authors

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Amélie Boulais, is the Head of Market Entry Strategy team at Sartorius. In this role, she determines the go-to-market strategy for the Viral-based Therapeutics segment, covering both vaccine and gene therapy applications. Amélie graduated from the ENSTBB (the Biotechnology Engineering Institute of Bordeaux, France) and holds a Biotechnology Engineer degree.

She started at Sartorius in 2008 as an Application Specialist for the purification technologies division. While in this role, she supported customers in the technical evaluation of purification technologies for protein and viral applications. She moved on to Process Development Consultant's role in 2015, supporting and advising actors of the bio-industry in their development from upstream to final filling operations. In 2016, she joined the Bioprocess Platform team, taking over the responsibility for vaccine applications.

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Piergiuseppe Nestola, PhD, is a Manager of Process Technology Consultants at Sartorius where he is responsible for providing scientific, technological and process leadership in the field of viral-based therapeutics. He holds a PhD degree in Chemical and Biochemical Engineering from Universidade Nova de Lisboa (PT), where he developed virus purification processes for vaccines and gene therapies.

Before joining Sartorius Piergiuseppe worked for several years at Janssen Vaccines AG in Bern (CH) as a scientist and team leader in the process development group. He was involved in developing and scaling up both viral vectors and protein-based vaccines in this role. Piergiuseppe has also been a judge at the Mass challenge and Bioexpert network incubators since 2018, supporting start-up life science companies.

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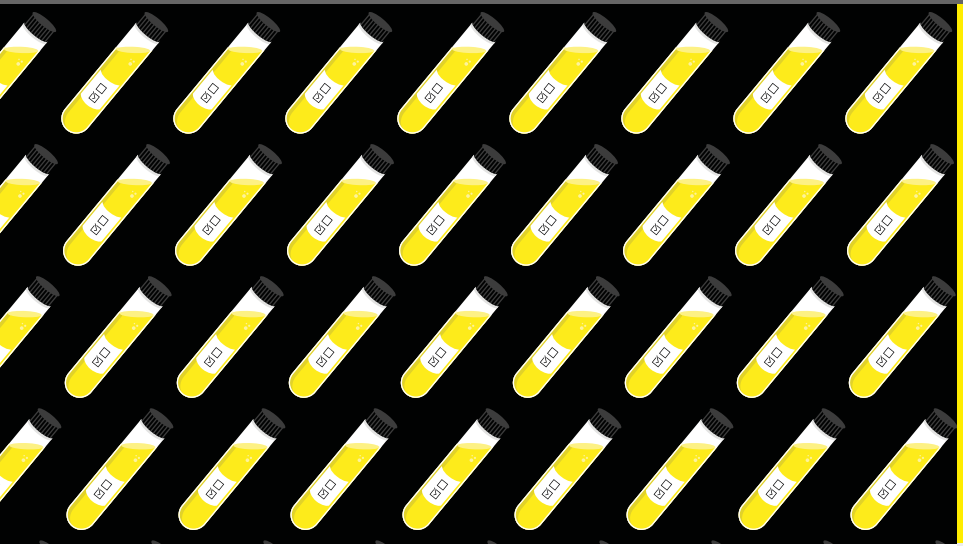

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Success at Speed: Digging into Accelerated Vaccine Development

Part 1 – The Need for Speed and Safety

As the world grasps the severity of the ongoing pandemic, we must ask how we can accelerate vaccine development safely – for COVID-19 and other therapeutic areas.

By Amélie Boulais, Vaccine Platform Marketing Manager, Sartorius, and Piergiuseppe Nestola, Global Vaccine Technology Consultant, Sartorius.

The Need for Speed and Safety

Immunology is not an exact science. There are still many aspects of the immune system that are not properly understood, meaning that vaccine success requires a number of attempts. On average, it takes 10 – 15 years to develop a successful vaccine. Challenges include identifying the right antigen to generate an immune response, developing the right manufacturing strategy to produce it at scale, and testing the vaccine in a large enough number of people to ensure efficacy and safety. As vaccines are used in large numbers of healthy people, extensive clinical testing is required, which is time (and money) consuming. Developers must measure vaccine response over time to see if long-term protection is offered, and side effects may only be seen when the vaccine is injected into large numbers of people. Consider dengue: when a vaccine was developed and began to see use in large numbers of patients, it was found that vaccination could lead to more severe cases of dengue in some patients. Such an example reiterates the need for extensive studies – and highlights the challenges of developing a successful vaccine. Although this example is not the norm in vaccine development, extensive studies are always required to ensure safety.

The first authorization for an Ebola vaccine was for emergency use only, prior to finalizing its clinical evaluation – a move that is typically used when the risk-benefit ratio of using an unapproved drug appears to be in favor of benefit, such as during a pandemic. With regards to COVID-19, there are ongoing discussions taking place in regulatory agencies, and so perhaps we will see a new framework created to cover pandemic vaccines.

The Need for Speed

It is essential to take the time to evaluate efficacy and safety during vaccine development, but it is possible to accelerate the timeline. At present, the industry is looking to develop a vaccine for COVID-19 in 12 – 18 months. Is this possible? Perhaps. Will it be a challenge? Absolutely.

First of all, the funding for pandemic vaccine development will be a considerable challenge. It takes about $1 billion to make a vaccine. But right now, we don't know which candidate and which approach is best, so resources must feed them all. →

When it comes to manufacturing, there are a range of ways in which developers can safely accelerate processes.

The Key Word Is Technology. Our Top Tips Are:

01. Rely on partnerships – including those with service providers.
We will not find a solution by working in silos and the industry must connect quickly. Start-ups and universities have expertise and promising vaccine candidates; established vaccine manufacturers have experience in running clinical trials and regulatory filings; contract manufacturing organizations have production capacities; critical suppliers have the capacity to ensure quality supply.
For example, Sartorius can offer services, such as cell banking and testing, cell line development assay developments, to ensure the development of a safe process right from the beginning.

→ Small start-ups and universities do not have the funding to develop candidates – and even the established players of the vaccine industry are taking a big risk before the outcome of clinical trials. Funding organizations, including not for profits, governments, and private corporations, will be critical to support this global health initiative.

We also need to consider the fact that our understanding of SARS-CoV-2 is still growing – and important questions do not have definite answers. Are patients immune from reinfection after contracting COVID-19? Is the virus mutating substantially? What percentage of the population has been infected? Why do some people develop cytokine storms? Who is most at risk? Who should be vaccinated first?

Despite incomplete or missing answers, there are well over one hundred vaccine candidates in development all over the world and this number is expected to grow in the coming months. Some candidates are already moving into phase 3 clinical trials. The race to a vaccine is like a marathon; the runners are all very close to one another at first, but as the race goes on certain groups will start to pull ahead – and hopefully at least one of them will make it to the finish line! Companies can accelerate development in many ways, while still respecting safety and efficacy. In traditional vaccine development, the different steps are usually sequential, but now they are happening in parallel – with production of a vaccine commencing even before the outcome of a clinical trial is known, to ensure readiness for distribution once approval is given. Clinical phases are also happening in parallel, with some beginning before the previous one ends. Patient recruitment for trials needs to be rapid, and the results must be communicated to all stakeholders quickly. →

02. Focus on single-use technologies.
They are much faster and cheaper to implement at large scale than stainless steel technologies (delivery and installation is faster, validation is faster, capex is lower) and offer flexibility to adjust production to demand. For example, you can invest first in a 2000 L bioreactor, and add another one later if required – or scale down to 500 L. You can also repurpose existing single-use equipment. Established suppliers of single use equipment, like Sartorius, have a strong supply chain and a reputation for quality – and this is important when speed is of the essence; you need to be able to trust your suppliers.

03. Ensure your analytical assays are properly validated.
Analytical development is the most critical piece of the puzzle because you need to ensure the quality of your drug product.

→ To accelerate development safely, manufacturers will need to have regular meetings with regulatory authorities to discuss the next steps based on clinical outcomes, and the potential risk-benefit evaluations that must be considered. It may also be necessary to redesign clinical trials and perhaps consider challenge studies, but this latter point raises ethical concerns.

COVID-19 – and Beyond

A pandemic of this scale is a first for our modern world but, in reality, the scientific community has seen this coming for a long time. We live in a globalized world, with pockets of high population density. There is an enormous amount of global travel and the climate is changing. All twhe conditions are there for a pandemic. Influenza has been a potential pandemic threat for some time, spurring the vaccine industry to modernize its manufacturing processes by moving away from egg-based to cell culture-based production. However, the World Health Organization already identified the threat of a pandemic from another source – calling it "Disease X" – and the Coalition for Epidemic Preparedness Innovations (CEPI) was created specifically for this eventuality: to prepare for a pandemic and to support the industry.

Coronaviruses have also been previously identified as a pandemic threat. A paper from 2007 concluded: "Coronaviruses are well known to undergo genetic recombination (375), which may lead to new genotypes and outbreaks. The presence of a large reservoir of SARS-CoV-like viruses in horseshoe bats, together with the culture of eating exotic mammals in southern China, is a time bomb. The possibility of the reemergence of SARS and other novel viruses from animals or laboratories and therefore the need for preparedness should not be ignored." [1]

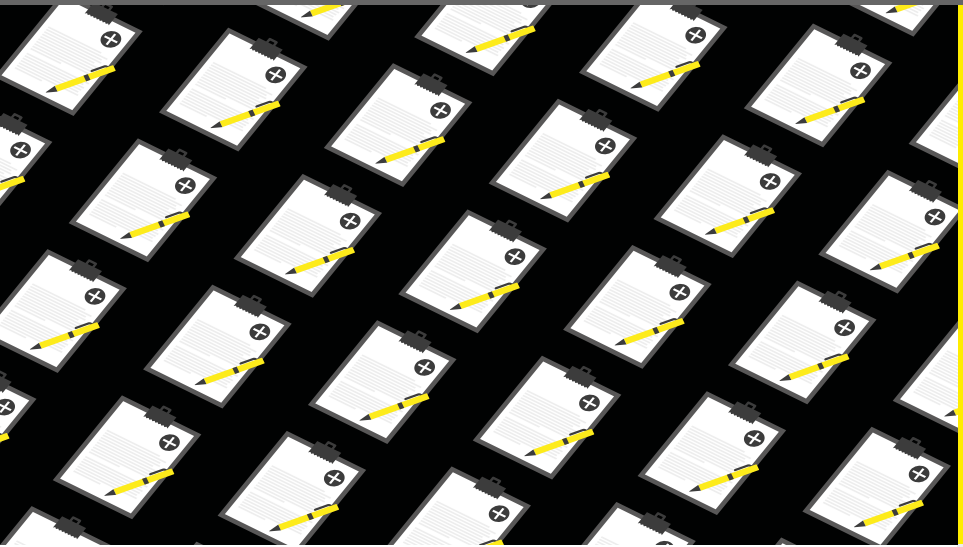
Although COVID-19 has become a clear focus for vaccine manufacturers, there are also many other therapeutic areas that should not be forgotten during the pandemic. For example, cancer vaccines and vaccines against unmet indications such as HIV, malaria, and RSV. There are also many existing vaccines that can certainly be improved upon, such as influenza (moving from egg-based to cell culture-based vaccines, developing a universal flu vaccine, and assessing pandemic readiness) and tuberculosis (improving the BCG vaccine). And all vaccines can benefit from faster development – because patients are waiting all over the world.

04. Make use of the increasingly digital world.
Tools such as design of experiment and multivariate data analysis (MVDA) software will help to accelerate scale-up and de-risk tech transfer, while ensuring process robustness. In addition, multivariate real-time monitoring can deliver continuous insight of your process and allow you to predict and correct deviation before it occurs. It helps to keep quality consistent, maximize efficiency and reduce cost – this is particularly important for COVID-19 because, when trying to accelerate development, companies will not have the number of batches required during normal development (for engineering runs, PPQ run, and so on). Therefore, it is essential for data generated during manufacturing to be used in a clever way to ensure that the manufacturing process is under control. Don't forget: the process is the product.

05. Discuss your strategy early on with regulatory authorities to get clear guidance.
Regulators are prioritizing COVID-19 programs and are very willing to engage with manufacturers.

Reference

[1] V CC Cheng at al., "Severe Acute Respiratory Syndrome Coronavirus as an Agent of Emerging and Reemerging Infection," Clin. Microbiol. Rev., 20, 660-694 (2007)



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Success at Speed: Digging into Accelerated Vaccine Development

Part 2 – Regulatory Considerations

It is well accepted that vaccine development needs to move faster, but what are the regulatory considerations and how can companies balance compliance and speed?

By Amélie Boulais, Vaccine Platform Marketing Manager, Sartorius, and Piergiuseppe Nestola, Global Vaccine Technology Consultant, Sartorius.

Regulatory Considerations

Out of all biopharmaceutical products, vaccines are subject to perhaps the most stringent regulatory oversight. This is unsurprising given that they are administered to enormous numbers of healthy individuals. The intense scrutiny of vaccines includes requirements for significant post-approval market surveillance.

Even before the emergence of COVID-19, it was widely accepted that vaccine development was slow. Depending on the country (or province), even clinical trial approval can take over a year. With such a focus on safety, the reality is that vaccine clinical trials will always be somewhat time consuming. However, efforts are being made to accelerate the process; some regulators, for example, offer fast-track designation, accelerated approval, priority review, or other similar frameworks for certain products. In fact, some regulators began considering the feasibility of accelerated vaccine development for a pandemic long before COVID-19. For example, the EMA put in place emergency procedures to speed up the assessment and authorization of a pandemic vaccine; it allows vaccines to be developed and authorized before a pandemic, but not marketed (this is known as conditional marketing authorization). Unfortunately, such preparedness does not apply when a pandemic pathogen is unknown. Meanwhile, the FDA has the power to grant emergency use authorization for certain products, if specific criteria are met.

Currently, however, there is no fully established regulatory pathway for pandemics caused by emerging infectious diseases. One structural gap is the lack of an explicit pathway for local regulators to leverage recommendations from larger regulatory authorities, such as the EMA and the FDA. Such a pathway could enable local regulators to benefit from additional regulatory authority expertise to reduce review and approval times of new vaccines at the country level. Right now, existing blockbuster vaccines can have more than 100 regulatory files; that's one for each country where the vaccine is distributed.

Some novel initiatives are being seen from other stakeholders; for example, the WHO's Solidarity Trial aims to accelerate the search for effective COVID-19 treatments.

The WHO has been working with numerous parties to develop clinical trial protocols that do not rely on placebo controls. That could help by:

01. Speeding up initiation of trials
02. Enabling comparisons between multiple sites and products
03. Streamlining data collection and processing
04. Establishing surrogate endpoints
05. Improving integration for regulatory submissions.

Other more controversial ideas have emerged to try to accelerate the process; for instance, the WHO is considering the use of human challenge studies (the controlled infection of volunteers with the SARS-CoV2 virus to verify vaccine efficacy) but these are subject to ethical consideration.

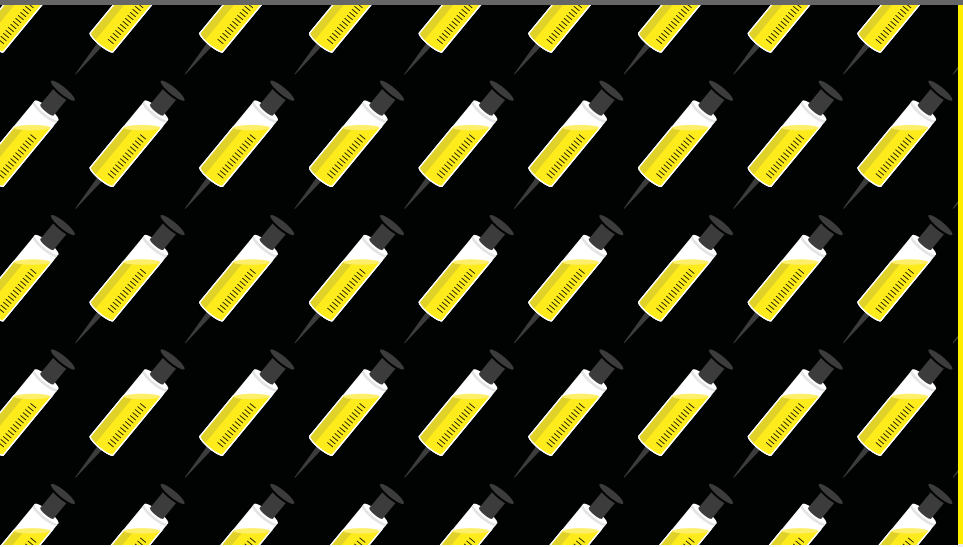
Rapid, but Efficient, Manufacturing

It will be down to regulators to learn from the COVID-19 pandemic and establish new frameworks, but sponsors themselves also have a role to play in helping to accelerate vaccine development safely by devising new ways to speed up recruitment, facilitate how trials are run, and develop efficient manufacturing processes. From a manufacturing perspective, it is crucial that moving fast does not jeopardize safety. When clinical trials are accelerated, the whole clinical material supply chain is under pressure, and process development needs to happen in a much shorter time frame. If an insufficiently robust and poorly understood process is transferred to GMP, it can lead to deviations and scalability issues. When moving fast, developers will also not have time to build a dedicated facility, instead "adapting" an existing manufacturing facility, which can lead to more risk. Knowing your critical process parameters (CPP) and critical quality attributes (CQA) will help when it comes to discussions with regulators (which should start early!), so it is imperative that the relevant data is well captured, using data analytics software and solutions.

→ Companies without manufacturing experience will likely need to find an experienced partner to help them develop a feasible and efficient manufacturing process. Right now, many start-up and universities are joining the race for a COVID-19 vaccine but, although the science may be compelling, their lack of experience of clinical trials and GMP manufacturing may slow them down. We frequently see how processes with incomplete development work result in poor GMP performance. In our view, investing in a process platform can give a competitive edge because you have more data and knowledge from previous vaccine candidates developed using that same platform. We also advise companies to make use of high-throughput screening tools.

For example, Ambr® can be combined with DoE software to assess design space early on. When moving into manufacturing, it is essential to use all of the data generated in the best possible way. Multivariate data analysis can be used to understand possible interactions between different CPP, which may not be obvious in a simple analysis.

Always remember that regulators not only look at clinical results, but also the robustness of the manufacturing process. Even when trying to move fast, do not neglect proper process development.



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Success at Speed: Digging into Accelerated Vaccine Development

Part 3 – Vaccine Modalities

Virus-based vaccines were our first foray into immunization, but the field had to move on, embracing recombinant proteins, and now viral vectors and mRNA vaccines.

By Amélie Boulais, Vaccine Platform Marketing Manager, Sartorius, and Piergiuseppe Nestola, Global Vaccine Technology Consultant, Sartorius.

Vaccine Modalities

Virus-based vaccines are the oldest form of vaccination, dating back to the 1700s, when Edward Jenner famously demonstrated how cowpox virus could provide immunity against smallpox. Created by producing and purifying an inactivated or attenuated version of the pathogenic virus, such vaccines have been used to combat many diseases, including rabies, polio, measles, mumps, rubella, and influenza. It's fair to say the approach has a long track record, but it's not perfect.

Traditional viral-based vaccines pose significant manufacturing challenges. The pathogenic virus has to be produced in large quantities to manufacture the vaccine, and some viruses, such as polio, rabies or SARS-CoV-2, are classified as biosafety level 3 (BSL3). The manufacturing process must also be tailored to the pathogen. For each new vaccine, you essentially start from zero, meaning long development timelines and the need to establish dedicated manufacturing facilities.

With the advent of molecular biology tools and increasing knowledge of immunity, recombinant subunit vaccines emerged. These vaccines consist of a recombinant disease specific antigen that can be recognized your immune system. Although development is simpler (manufacturers can begin with a well-known expression system) it is not a true platform approach. After all, the antigen expressed is unique and specific to the pathogen, and requires a tailored purification process. Furthermore, generating a strong T cell response can be challenging, although specific adjuvant can help.

Time for Vaccine Disruption

But what if we could turn the patient's own cells into mini-factories that pump out disease-specific antigen? Viral-vector-based vaccines and mRNA-based vaccines do just that and are considered disruptive approaches to vaccine production. Viral vector vaccines use genetically engineered viruses (for example, adenoviruses or poxviruses) to hijack the patient's cells into expressing antigen. On the other hand, mRNA-based vaccines deliver single-stranded mRNA molecules into the patient's cells (for example, via lipid nanoparticles), where they are translated into protein (antigen). →

→ These two approaches offer compelling advantages. Both safely mimic an infection (without a pathogen) and generate strong immune responses without the need for an adjuvant. And they are both true manufacturing platform approaches that can be applied to many different vaccines; the only aspect specific to the vaccine is the genetic code of the antigen.

Not only do such platforms speed development, they also offer significant manufacturing flexibility, as different vaccines can be produced in the same facility. mRNA-based vaccines also have the added advantage of being produced using cell-free processes, which keeps manufacturing relatively straightforward.

Overall, mRNA or viral-vector based vaccines offer significantly accelerated development timelines compared with viral or recombinant vaccines.

Tackling COVID-19

Researchers across the globe are exploring all four main modalities in the search for a COVID-19 vaccine; such a multi-pronged approach is sensible, as we do not yet completely understand the virus and the type of immune response it generates. Do we need a vaccine that generates a strong B cell response, a T cell response, or both? mRNA and viral vector vaccines usually generate a strong T cell response, while recombinant protein vaccines usually generate a strong B cell response. Early preliminary data indicate neutralizing antibody (B cell response) as a potential correlate of protection, and around 35 percent of COVID-19 vaccine candidates are using a recombinant subunit approach, with variety of expression systems, including bacteria, yeast, mammalian cell lines, and plants.

However, we can all agree that speed is of essence in this pandemic. And so the accelerated development and manufacturing timelines of platform approaches may mean that mRNA or viral-vectors reign supreme …

Remember that, prior to COVID-19, vaccines against SARS and MERS were in development, but aborted when the outbreaks were over. This highlights a significant problem in this field: vaccine development can be lengthy, but if it takes too much time then the outbreak may be over and the vaccine will have missed its biggest opportunity. If a vaccine is developed too late, it can hardly be considered a success – and its future is in doubt.

It is clear that we must learn how to safely and successfully accelerate vaccine development – not only for this pandemic, but also for the inevitable outbreaks of the future.

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Success at Speed: Digging into Accelerated Vaccine Development

Part 4 – Commercial Manufacturing

How to prepare for the rapid set-up of commercial manufacturing

By Amélie Boulais, Vaccine Platform Marketing Manager, Sartorius, and Piergiuseppe Nestola, Global Vaccine Technology Consultant, Sartorius.

Commercial Manufacturing

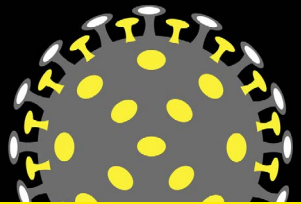
A typical vaccine takes around 10 to 12 years to reach the market, giving developers ample time to consider strategies for mass manufacture. A key question: "Where should we base production?"

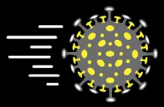
A company may plan to build a dedicated manufacturing facility in anticipation of a potential blockbuster (a risky approach – the vaccine could fail in phase III), or may decide to launch the vaccine out of the pilot facility.

Some vaccine manufacturers are now considering the use of flexible facilities that can accommodate the manufacturing of different vaccine types, depending on the demand, which is a challenge given the variability of current legacy vaccine processes. →

The World is Waiting for a Vaccine

Given that there is no time to build new facilities, there are two options





Use existing facilities from established vaccine manufacturers.
This option sounds good in theory, but there is limited capacity available – and a limited number of established vaccine players on the market. Companies like Sanofi, MSD, Pfizer, GSK, or the Serum Institute of India have production facilities dedicated to specific vaccines, but these facilities are not really flexible and the capacity to rapidly switch production to a potential COVID-19 candidate is limited. Moreover, these facilities are already producing important vaccines, and you don't want to jeopardize their supply either; in other words, you don't want to block COVID-19 only to create a polio or measles outbreak because of a supply limitation.

Benefit from the production capabilities and expertise of CDMOs.
Partnering with a CDMO can ease capacity constraints in house and allow a company to respond more quickly to changes in demand. There are hundreds of CDMOs across the world – and the potential to localize manufacture by different geographies. This network could help the industry to produce the first-generation COVID-19 vaccines. A variety of vaccine approaches are being taken to address COVID-19, but most rely on recombinant proteins, viral vectors or mRNA – and many CDMOs have expertise in this area. It may be more challenging, however, to find CDMOs capable of working with inactivated or live attenuated vaccines in a BSL3 environment.

→ Many new collaborations involving vaccine developers and CDMOs have been announced since the pandemic began – and we will likely see many more as vaccines begin to reach later trials. If you are going to go down the CDMO route, we recommend taking the following into account when choosing a CDMO to mitigate risks:

1. Consider the CDMO's expertise in your chosen vaccine platform (viral vectors, mRNA, recombinant protein, expression system, and so on). This point is crucial! You need to decide on the elements of the vaccine journey you wish to hand over to the CDMO – such as process development, manufacturing, downstream processing, packaging, regulatory approval, distribution, and so on. Consider the CDMO's successful track record in all these areas.
2. Verify the CDMO's ability to produce in time – and check how they will achieve this goal. Will they work with third partners? Do they already have all the necessary equipment in place? Evaluate both the manufacturing capabilities and any potential sources of delay.
3. Understand the CDMO's experience in vaccine production. You should also examine if they have been adequately inspected by local or major health authorities. Some CDMOs are willing to share risks – and it's a good sign if a CDMO proactively suggests ideas to mitigate risks for the project.
4. Decide how you want the collaboration to look. Will you hand over the project completely, or do you prefer to be involved in each step? Addressing communication and project management is also crucial.

Process development must also move at lightning speed

In our experience, there is a direct correlation in process complexity versus issues in manufacturing. And so, we recommend a manufacturing process that is as simple as possible to help both smooth and accelerate scale up. Having a limited number of buffers or chromatography unit operations, for example, can offer dramatic advantages during scale up and commercial manufacturing.

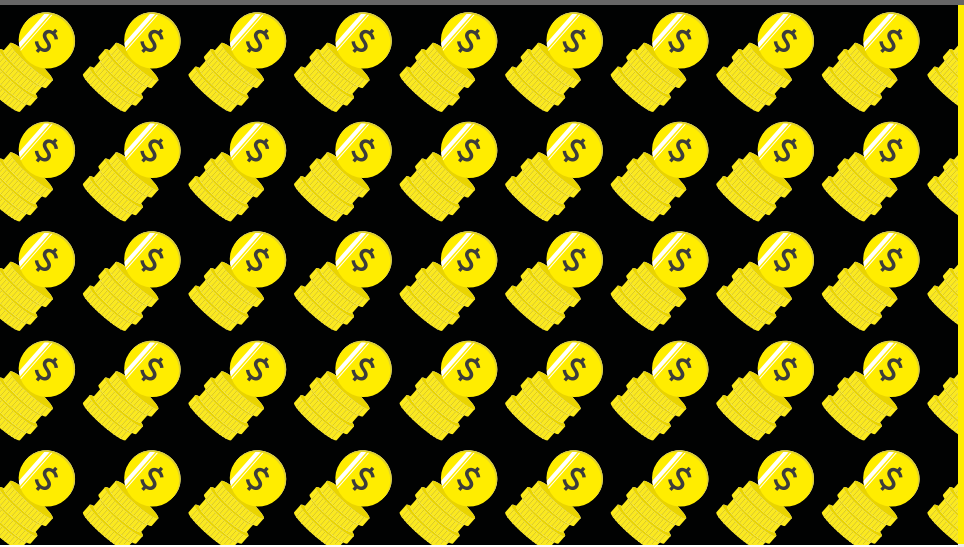
Speed of manufacturing is also affected by the understanding of critical process parameters (CPPs). When scale up fails, it is often because process development was not performed properly or the CPPs were not well understood. →

→ A deep understanding of the CPPs will also aid tech transfer. It is not always possible to use the same equipment or consumables when transferring manufacturing to a new location – particularly during a pandemic when there isn't time to perfectly replicate the original manufacturing set up. But if you understand your CPPs, you should be able to correctly assess the risks and modify the manufacturing process without affecting final drug product quality.

mRNA vaccines that can be manufactured using platform technologies have the potential to be scaled up very quickly, particularly given the straightforward unit operations. Viral vectors also have advantages in terms of speedy scale up because their downstream processing operations have significantly less unit operation compared with recombinant subunit processes, where two or three chromatography steps are generally required. Whatever type of vaccine you are making, you need to prepare for mass manufacturing early. You need to consider the supply chain, ensuring you have the right quantities of raw material for manufacturing and the right distribution network in place to get the vaccine to patients. And you need your large-scale equipment in place early. Large-scale equipment tends to have long lead times so engaging in early discussions with suppliers is important. And it's worth considering single use, which can be deployed more rapidly than stainless steel.

With single use, it's possible to get a facility up and running in 12 months as opposed to the 24 months required for stainless steel. In terms of COVID-19, however, this is still slow. The world is waiting for a vaccine.

There are many paths that can be taken to help accelerate speed to commercial manufacture of a vaccine. If you are unable to use existing facilities and aren't prepared to invest in a new single-use facility, then a CDMO can offer significant benefits – including expertise and production capabilities. Choose your partners carefully and once you find the collaboration that works for you, make sure they have a good understanding of your product in the early stages of process development. If your manufacturing partner is ready to hit the ground running when you need to get moving with mass manufacturing, you'll be able to bring your vaccine to patients much sooner.



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Success at Speed: Digging into Accelerated Vaccine Development

Part 5 – Reducing Costs

Global access to the vaccine is essential to provide protection against the virus. A big hurdle to accessibility will likely be price. They key is to strike a balance between price and development costs.

By Amélie Boulais, Vaccine Platform Marketing Manager, Sartorius, and Piergiuseppe Nestola, Global Vaccine Technology Consultant, Sartorius.

Reducing Costs

For COVID-19, we do not yet know which pricing tiers or strategies will be adopted. What we do know is that, generally speaking, many factors influence a vaccine's final price tag. Key questions include: Which country is the primary target for the vaccine? What value will the vaccine add to the healthcare system? How effective is the vaccine? And, of course, how expensive is the vaccine to develop and manufacture? A vaccine that is expensive to make will typically have a much higher price tag.

Vaccine manufacture requires a number of unit operations, a specialized workforce, dedicated manufacturing space, and the vaccine must be extensively tested for quality control. Fill-finish operations are also very expensive – particularly when using pre-filled syringes (note that some COVID-19 vaccine developers are considering multidose vials to help cut down on costs).

A good chunk of the costs are modality agnostic; whatever the vaccine platform, the developer will need to conduct large clinical trials (at least 30,000 participants for phase III), quality assurance, and fill-finish activities. However, some costs do relate to the modality and complexity of the manufacturing process. The production of viruses or recombinant proteins is expensive, as it relies on cell culture or fermentation steps, followed by a complex downstream process. And that's one reason why there is growing industry interest in newer platform modalities, such as mRNA, which can be manufactured using cell-free (and thus simpler) processes →

→ Different modalities also have different manufacturing yields and therapeutic dose requirements. Most of the current COVID-19 vaccines in development are expected to require two therapeutic doses in a "prime and boost" regime. It is important to align the manufacturing process to the dose requirements; cost analyses show a strong relationship between cost per dose and cost of goods, influenced by productivity, final yield, and therapeutic dose. Put more simply, if the selected vaccine platform requires a high therapeutic dose, but the productivity of the vaccine manufacturing process is low, then the overall cost per dose will be very high.

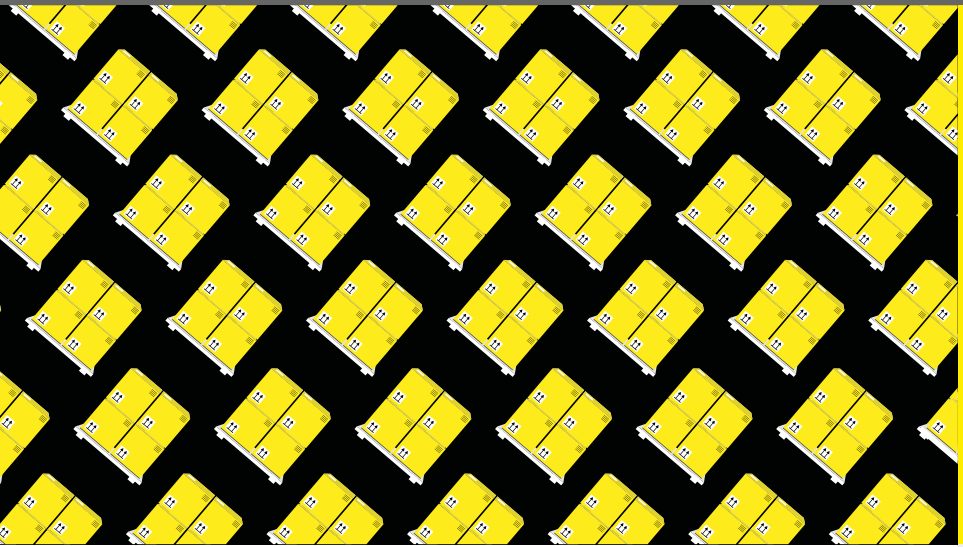
The therapeutic dose can potentially be minimized – and therefore costs saved – by changing the drug delivery method. Syringe and needle are standard, but can be an expensive part of the value chain. What about mucosal delivery (nasal spray) or transdermal (skin patch) options? Both have the potential to reduce the therapeutic dose.

Fixed costs can also be reduced by using single-use technologies, which shifts capital expenditure into operating expenditure, while also simplifying validation and cleaning, and helping to reduce the potential for cross contamination.

Moreover, manufacturing platforms such as mRNA or viral vectors can ultimately be used to develop different vaccines, which means the development costs of the platform can be shared across multiple products. This is important because, beyond COVID-19, the success rate for vaccine development is generally low, which means that one successful vaccine has to not only cover its own development costs, but also the costs of development for all of the previous vaccines that have failed. This is why vaccines can come with high price tags.

Finally, let us remember that quality is not always the enemy of cost; many elements that contribute to a good manufacturing process can actually result in savings. For example, focusing on process optimization and increased process understanding can reduce batch failure rate – saving costs.

For patient access and return on investment, it is great to consider the options and proactively drive down costs, but we must not sacrifice safety or speed in the process.



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Success at Speed: Digging into Accelerated Vaccine Development

Part 6 – Logistics and Global Availability

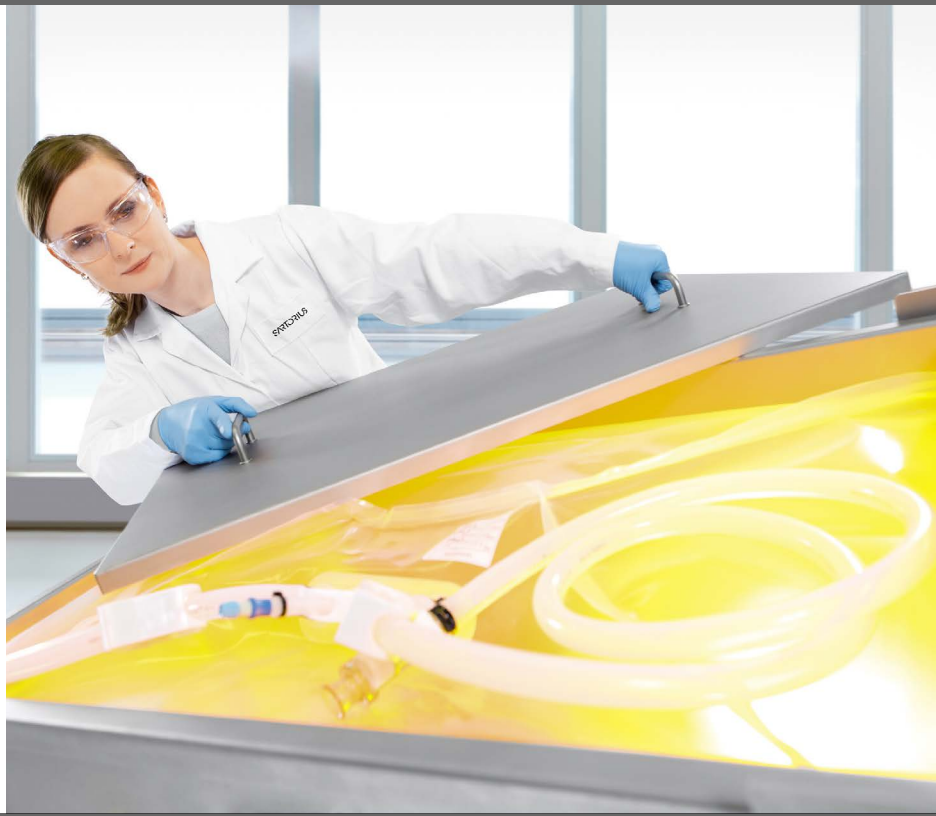
A vaccine must be able to reach patients who need it. Reliable partners and procedures are a must.

By Amélie Boulais, Vaccine Platform Marketing Manager, Sartorius, and Piergiuseppe Nestola, Global Vaccine Technology Consultant, Sartorius.

Logistics and Global Availability

The sensitive nature of vaccines, coupled with the fact that some countries may not have reliable infrastructure, can make distribution challenging. Environmental conditions across the supply chain can degrade potency. To offer some well known examples, heat-sensitive vaccines include the oral polio vaccine (OPV) and measles, mumps and rubella (MMR); those sensitive to freezing include hepatitis B, human papillomavirus (HPV), and influenza. Other vaccines are sensitive to light, such as Bacillus Calmette–Guérin (BCG) for tuberculosis, and MMR.

Generally speaking, live vaccines (bacterial or viral) are particularly prone to potency loss through higher temperatures, and their stability is often comprised already at room temperature. Whereas, non-live vaccines (inactivated, proteins) are more stable in higher temperatures, but are often more sensitive to freezing because they contain adjuvants (salt aluminium, for example, can collapse during freezing).



→ The unique characteristics of the vaccine platform and formulation will determine the required storage conditions, and the resulting range of optimal temperatures is significant. Some vaccines must be stored at around 2–8 °C, whereas others require temperatures as low as -80 °C (particularly challenging to maintain during distribution). Clearly, improving the thermostability of a given vaccine can pay dividends when it comes to later logistics and cold chain management. Some "new generation" vaccines behave differently to the classic vaccines noted above and can be much less sensitive to environmental conditions[1]. Thus, combined with advances in formulation development, it is now possible to create vaccines that are stable even at room temperature. Recent research has also indicated that certain mRNA formulations maintain stability at room temperature[2].

Whatever the vaccine, any transportation method must be validated and carefully monitored as part of the global GMP requirement to validate the drug process. ASTM and ISTA offer standard guidelines for shipment testing and the WHO recommends electronic monitoring. Notably, you should not only consider the shipping method for your final drug product, but also any transport required for the drug substance; for example, to a separate fill | finish facility. Accidental rupture of bags or container breakage can occur, and so it is crucial to ensure that any shipping materials are able to withstand the various forces that may occur along the journey. For the same reason, it's important to use reliable (and knowledgeable) shipping partners. Ultimately it is a combination of material, experienced partners and digital monitoring that can ensure that the quality of the drugs is preserved during shipments, and that the drugs keep their potency when delivered to the patients.

When addressing security risk for drug distribution, additional factors have to be taken into account: counterfeit drugs and stolen material. The pressure to get vaccines may attract the lust of people trying to make money with fraudulent drugs. Serialization is a good answer for better controlling the drug supply. The choice of reliable transportation partners is a must to avoid thefts of drugs during their distribution journey.

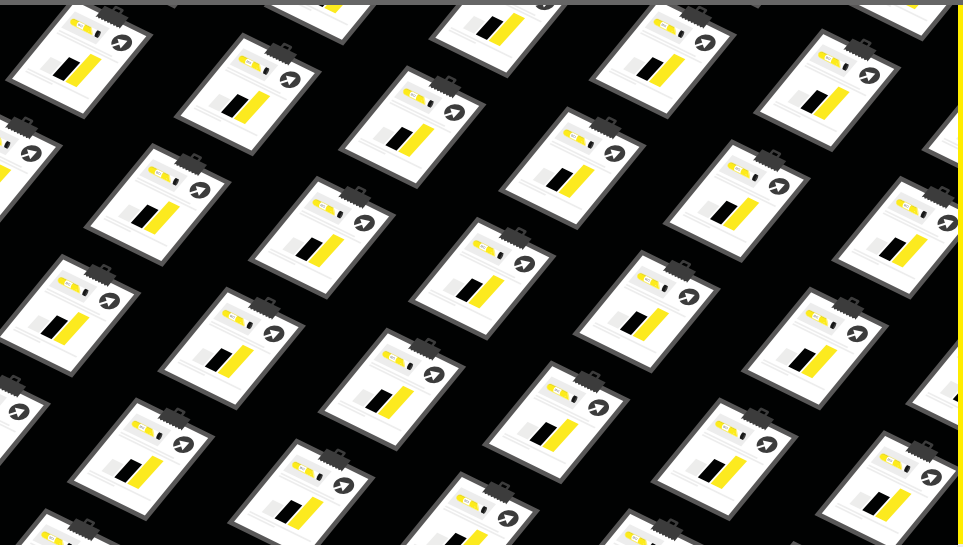
Vaccine production has historically been centralized by a few key manufacturers, but the trend is shifting. After all, centralized manufacturing can be risky; if there is a problem at the main plant, disruption of global distribution of the vaccine ensues.

Looking to better guarantee availability of routine vaccines, such as diphtheria, pertussis and tetanus (DTP), MMR, polio, and influenza, governments around the world have been actively funding local manufacturing capacity, which will certainly have an impact on logistics. COVID-19 has made the threat of disruption even more real – and it has also introduced additional challenges. Companies are already taking orders from governments for vaccines that are still in development. Assuming success, there will ultimately (and suddenly) be a high request for rapid vaccine shipments. In this regard, diversified supply chains and localized production will likely offer significant benefits.

References

[1] U Kartoglu, J Milstien, "Tools and approaches to ensure quality of vaccines throughout the cold chain," Expert Review of Vaccines, 13 (2007).

[2] C Zhang et al., "Advances in mRNA Vaccines for Infectious Diseases," Front. Immunol., (2019).



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Success at Speed: Digging into Accelerated Vaccine Development

Part 7 – Progress Over Time

There is a promising pipeline of vaccine candidates, but what happens if the frontrunners fail?

By Amélie Boulais, Vaccine Platform Marketing Manager, Sartorius, and Piergiuseppe Nestola, Global Vaccine Technology Consultant, Sartorius.

Progress Over Time

So far, the progress towards a COVID-19 vaccine is, frankly, incredible. In just nine months (January–September), more than 150 vaccine candidates have entered the pipeline – 35 of which are under clinical evaluation in humans, according to the latest WHO report[1]. Nine vaccines are in phase III trials and will be tested in large numbers of people (usually around 30,000), and three vaccines are already approved for limited use; two in China and one in Russia. All vaccine modalities mentioned in the previous articles in this series have made it to clinical evaluation: recombinant subunit vaccines, viral vector vaccines, viral vaccines, and mRNA and DNA vaccines. Great progress has also been made in terms of quickly scaling up manufacture, finding capacity, and forming alliances. Efficiency has been maximized in R&D, manufacturing, and clinical development to ensure a fast response.

To ensure availability of vaccines for their populations, many governments have already ordered millions of doses of the frontrunner candidate vaccines. For example, Europe has ordered 400 million doses of the AstraZeneca vaccine. The company is expecting to produce two billion doses and is partnering with companies all over the word to expand capacity. Another example is BioNtech, which has developed an mRNA vaccine and partnered with Pfizer and Fosun Pharma to ensure production and distribution. The US government has ordered 100 million doses, with an option for 500 million more, and Japan's government has ordered 120 million doses.

Despite the need for speed, clinical development must not compromise on safety or quality – as we have reiterated in this article series. Even though the timelines for COVID-19 vaccines are compressed, clinical trials phases have not been skipped, but rather companies are trying to combine phases and maximize efficiency in data gathering and analysis. Some companies, like J&J, are also enrolling more patients than typically required (currently at around 60,000 participants) for vaccine studies to ensure safety and to develop a reliable dataset[2].

Ultimately, most companies are aiming to be either first in class or best in class with their COVID-19 vaccine; both are difficult to achieve in the highly competitive first-generation COVID-19 vaccine race.

→ With companies taking every precaution to ensure safety, the primary danger of acceleration is perhaps more business related than public health related. Vaccine developers stand to make significant financial losses – particularly if production has already begun – if their clinical trials fail. And that's why the support of funding organizations is fundamental. Indeed, the large amount of funding available has facilitated the start of manufacturing or large-scale clinical trials facing business and financial risks.

There are a number of frontrunning vaccines right now, but if all are unsuccessful, the world will need to look elsewhere in the pipeline and move funding and partnerships to potential candidates at earlier stages of development.

When (or "if" for pessimists) a vaccine is successful, it will not offer 100 percent protection in a population. Right now, some pre-clinical studies suggest that, although COVID-19 vaccination of young subjects can prevent diseases of the lower respiratory tract, the virus is still present in the higher respiratory tract. And that means the virus can still circulate. Scientists also acknowledge that a vaccine may be less effective in the older population (which is already the case for flu vaccines, for example), who are more at risk of COVID-19 complications[3,4,5].

Different countries have different perceptions of the benefits and the risks. The public in most Western countries expect vaccines to protect as close to 100 percent of the population as possible, with no side effects – an incredibly high benchmark.
For many years, the anti-vaccination movement has been growing in strength so it will be crucial to reassure people that a COVID-19 vaccine is safe and efficacious. In other parts of the world, where access to healthcare is more difficult, governments may accept a vaccine that, while not protecting all people, will decrease the burden on healthcare systems. Currently, the FDA bar for approving a vaccine is to have at least 50 percent efficacy, which might be already good to release the burden on the intensive care departments.

For COVID-19 vaccines, any rapid approval will likely only be for emergency use until additional safety and efficacy data are available. Ultimately, any vaccine will only see global use if it is safe and effective, and when the benefits outweigh any potential risks.

References

[1] WHO, "Draft landscape of COVID-19 candidate vaccines," (2020).
Available at https://bit.ly/2EnMowJ.

[2] The Wall Street Journal, "For Covid-19 Vaccine, J&J Plans 60,000-Subject Pivotal Trial," (2020).
Available at https://on.wsj.com/3jKGKUY.

[3] Nature, "What the immune response to the coronavirus says about the prospects for a vaccine," (2020).
Available at https://go.nature.com/3iHa25l.

[4] Science Translational Medicine, "Criticism of the Oxford Coronavirus Vaccine," (2020).
Available at https://bit.ly/3iK3a7s.

[5] STAT, "The world needs Covid-19 vaccines. It may also be overestimating their power," (2020).
Available at https://bit.ly/34lX8ii.

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Success at Speed: Digging into Accelerated Vaccine Development

Part 8 – Lessons to Be Learned

What have we learned from the pandemic and how can we address the coming challenges?

By Amélie Boulais, Vaccine Platform Marketing Manager, Sartorius, and Piergiuseppe Nestola, Global Vaccine Technology Consultant, Sartorius.

Lessons to be Learned

The average vaccine, taken from the preclinical phase, requires a development timeline of around 10.71 years and has a market entry probability of 6 percent[1]. So far, however, we are confident that we can develop a vaccine against COVID-19 much faster.

The industry has developed a strong pipeline of more than 300 candidates, relying on diversified strategies and platforms. From a statistical point of view, 18 of them should make it to the market! On the other side of the coin, many candidates will likely fail; we've already witnessed sharp intakes of breath at the potential side effects of AstraZeneca's frontrunning vaccine.

Clinical trials are often halted because of adverse events that needs to be investigated before trials can continue, so the AstraZeneca pause should come as no surprise. However, it does emphasize just how difficult phase III can be.

Has COVID-19 changed the pharma industry – and vaccine development – forever?

Yes and No

The world has changed, with daily life affected and disruption across the globe. COVID-19 has demonstrated how important investments in vaccines are, and will likely lead to an increase in global capacity for vaccine production. In the future, we will no doubt see vaccine makers getting more involved in preparedness initiatives – and for sure, a rich pipeline for a universal coronavirus vaccine[2].

The industry has demonstrated remarkable agility and perseverance thus far in bringing promising COVID-19 vaccines and treatments to the clinic – and there has been unprecedented collaboration.

At the very beginning of the outbreak, the genome of SARS-CoV-2 was sequenced and shared by scientific communities, so that vaccine developers could get to work. Our feeling is that the pharma industry will return to business as normal once the COVID-19 pandemic is over. The big difference may be the emergence of dedicated groups and funding availability – inside companies or as part of industry organizations – who will continue to work on pandemic preparedness.

We should never forget what the industry can accomplish when we all work together.

Even if a vaccine is approved quickly, there are still challenges to face:

- Meeting demand. A recent survey from the Coalition for Epidemic Preparedness Innovations (CEPI) estimated that the global manufacturing capacity for a COVID-19 vaccine in 2021 is 2–4 billion doses, but the world may need 8–16 billion doses (assuming two doses per person). As a comparison, the total global annual production of commercial vaccines is about 20 billion doses. A target of 2–4 billion doses is already ambitious. And if we re-purpose some facilities to produce the COVID-19 vaccine, we will stop the production of other vital drugs. And we simply do not have time to build large dedicated facilities to meet short term demand.

- Ensuring a robust supply chain of all necessary equipment | consumables | materials. What happens when the orders of vaccine manufacturers exceed supplier manufacturing capacity? We all heard about the bottleneck of glass vials, for example, and it's possible that there will also be bottlenecks in syringes and packaging.

- Defining who gets the vaccine first. The COVAX initiative has been launched by CEPI, Gavi and the WHO to ensure equitable access to COVID-19 vaccines and end the acute phase of the pandemic by the close of 2021. But governments are placing huge orders for vaccines. If there aren't enough doses for everyone, then we may need to decide who should have priority – a provocative topic.

- Ensuring worldwide distribution. Are global supply chains robust enough to transport the vaccine everywhere it is needed – including those countries that lack infrastructure and cold chain?

We must analyze these challenges and find the right solutions – and ensure that new protocols are ready for when the next pandemic occurs. Global pandemics are now a question of "when", not "if." We were not ready for this pandemic. There have been many initiatives in the past aimed to improve pandemic preparedness – the foundation of CEPI being a key initiative – but none of this was enough. It has also become apparent that regulatory approval processes were not ready for accelerated vaccine development and have needed to be adjusted during the crisis.

We now all understand how quickly a virus can spread. It is critical to have a pipeline that targets viruses with the potential to create pandemics and we need to fund scientists working in relevant fields. The importance of vaccine platforms, such as viral vectors and mRNA, have also established themselves as critical for ensuring speed to the clinic.

References

[1] ES Pronker et al., "Risk in Vaccine Research and Development Quantified," PLoS One, 8 (2013).

[2] LT Giurgea et al., "Universal coronavirus vaccines: the time to start is now," npj Vaccines, 5, 43 (2020).

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