

How Pandemics and Outbreaks Have Influenced the Adoption of Single-Use Vaccine Manufacturing

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In just the last decade, infectious disease experts, public health organizations, governments and the biopharmaceutical industry have had to mobilize quickly in response to outbreaks and pandemics of H1N1, Influenza, Ebola, MERS, Zika and now SARS-Cov2 (Covid-19). While therapeutics are an immediate need, vaccines are the ultimate response in the fight against emerging infectious diseases. Unfortunately, vaccine development typically requires many years, and manufacturing large doses in an emergency remains a significant challenge. Preparing manufacturing plants to make a new vaccine can cost anywhere from \$50 million to \$700 million, according to a 2017 paper in *Vaccine*.ⁱ

To reduce the risk of such a major investment, biopharmaceutical companies typically wait until a vaccine is in the advanced stages of testing, with promising results, before starting to manufacture it in large quantities. This conventional development strategy compresses during a pandemic (Figure 1). Bruce Gellin, president of global immunization at the Sabin Vaccine Institute noted in a Wall Street Journal article that *“in a pandemic, you can’t wait to start making your investment in the manufacturing until you’re sure you have a product.”*ⁱⁱ

Outbreaks & pandemics are game changers

Phases overlap and development time is condensed

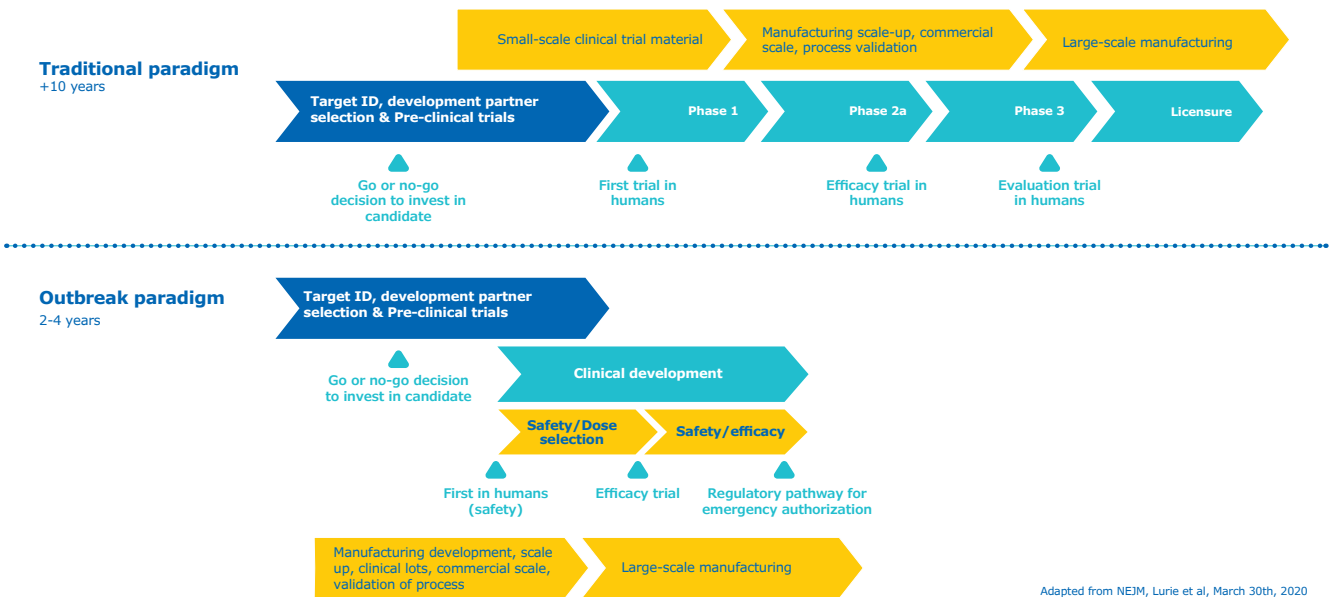


Figure 1. Comparison of the traditional vaccine development process with that needed during a pandemic. This accelerated timeline requires compression of the manufacturing process and a shift from a linear sequence of steps to activities being executed in parallel. *Adapted from Lurie, et al. NEJM March 30, 2020.*

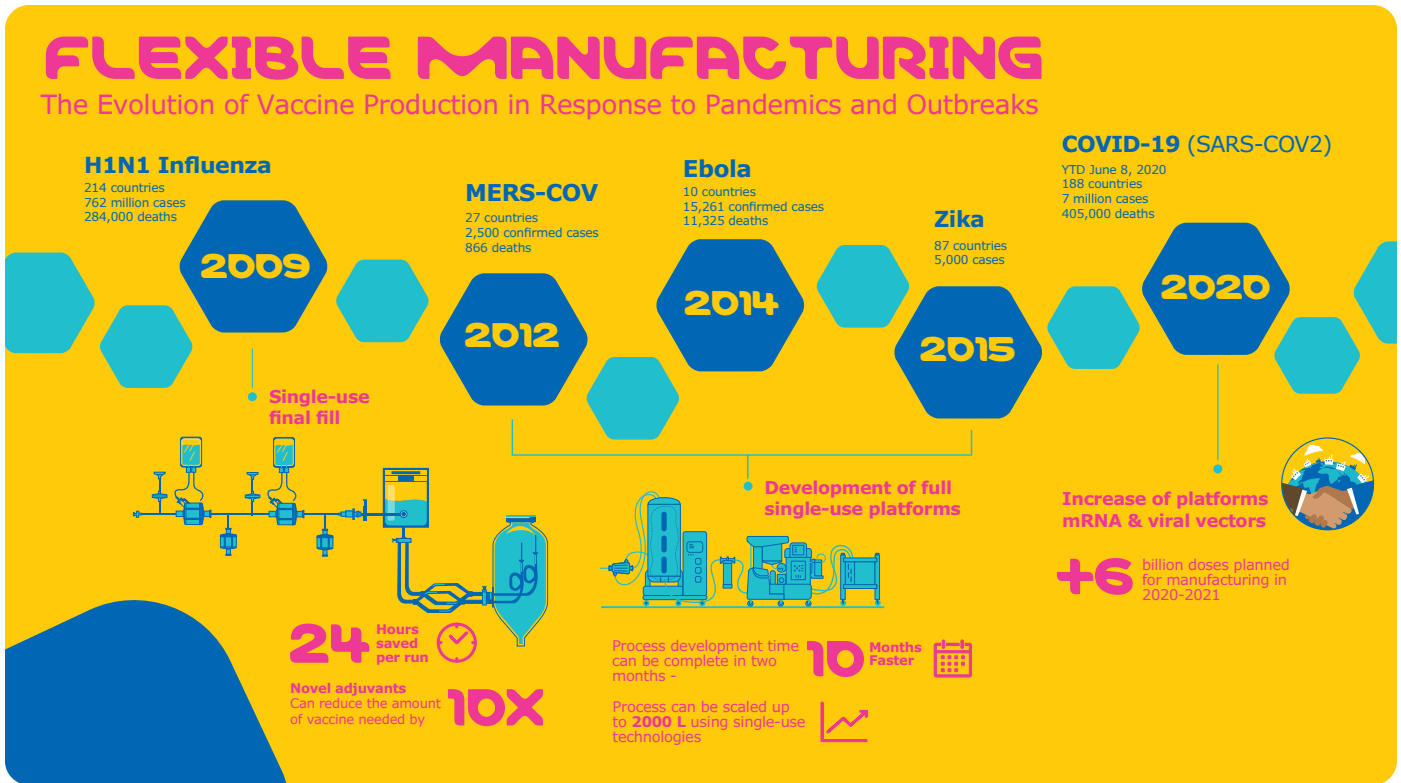


Figure 2. History of modern outbreaks and pandemics and the rise of flexible manufacturing.

During a pandemic, time is of the essence, and the need to move quickly drives important innovations in vaccine development and manufacturing. These advances help to compress the time from bench to bedside and include increased flexibility in manufacturing through adoption of single-use technologies, capacity mitigation and use of novel adjuvants and platforms such as DNA and RNA vaccines.

This rapid pace is exemplified by Moderna’s mRNA-based SARS-CoV-2 and CanSino’s adenovirus-based vaccine candidates which entered Phase 1 clinical trials less than ten weeks after the first genetic sequences of the virus were released. Despite that, there are still many questions about the capacity to produce Covid-19 vaccines at a global scale.

This white paper explores the impact of recent outbreaks and pandemics on the advancement of manufacturing technologies that have helped accelerate and improve our response to subsequent emerging biological threats and how vaccine manufacturing must evolve to increase global capacity and pandemic preparedness (Figure 2).

1. Early Adoption of Single-Use Technologies in Vaccine Manufacturing

The vaccine industry has pioneered the use of single-use technologies in manufacturing to resolve biohazard and contamination risks, especially when handling live attenuated microorganisms or when aseptic processing is required.

To meet the surge in demand during the 2009 H1N1 2009 pandemic, we partnered with a global vaccine manufacturer seeking to increase the speed and efficiency of its filling-unit operations without increasing the manufacturing footprint.

Traditionally, fill-finish machinery are fixed systems, which are comprised of complex components requiring assembly, cleaning and sterilization, disassembly, and material storage after filling is complete. Those operational steps allow for an open flow path, creating the possibility of contamination or sterility breach and subjecting operators to hazardous materials. Time-pressure and piston-pump systems are the predominant methods for dosing and filling. They require assembly, open flow paths, and validated clean-in-place (CIP) and/or steam-in-place (SIP) protocols to ensure a high probability of sterile final-product flow paths.

As a result, traditional fill-finish facilities are relatively inflexible, labor-intensive, involve long change-out times, have high operating costs, lengthy validation and training on procedures.

The manufacturer’s original process involved a restricted-access barrier (RAB) unit and standard stainless-steel process lines with *in situ* installation requiring CIP/SIP. The multidrug facility had installed hardware connected to hard-piped connections, limiting operational flexibility.

With the move to single-use technologies, the hard-pipe, time-pressure filling module remained in place, but was not used for this filling operation because of the time requirements of validation and operational cleaning; it remained in place for filling legacy products.

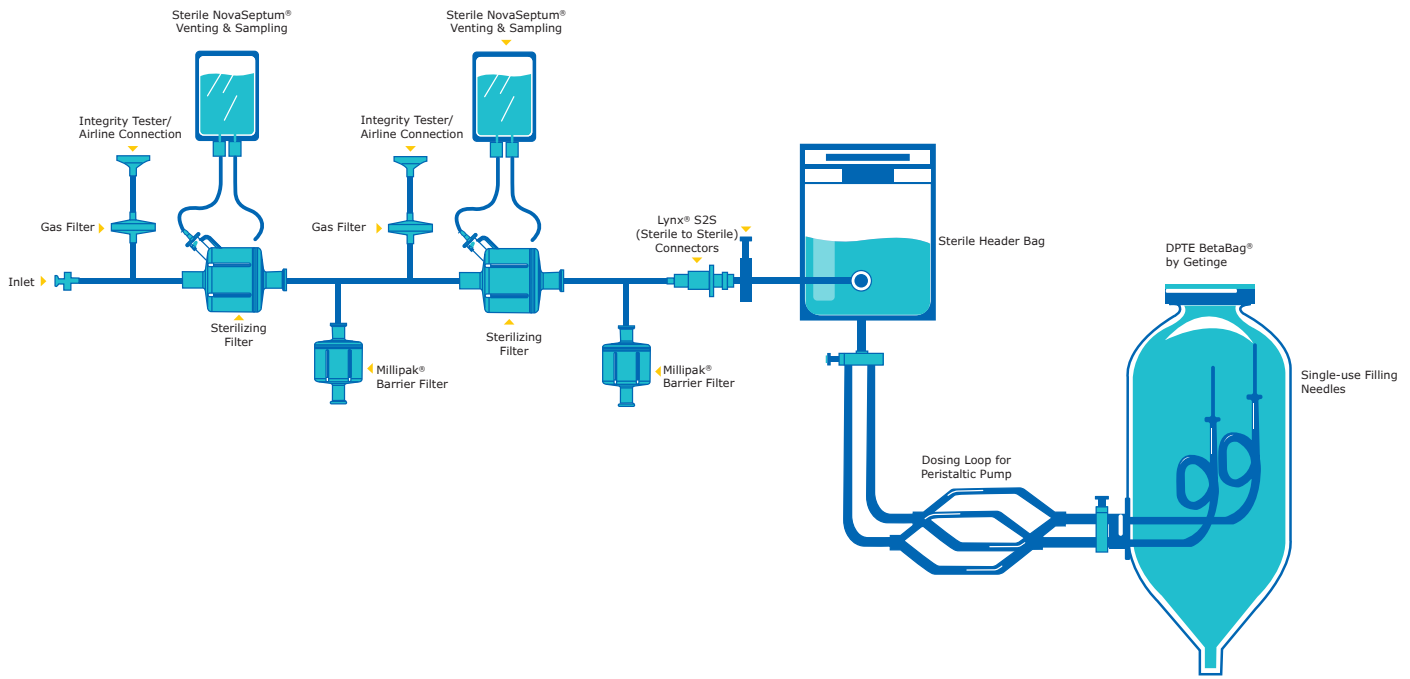


Figure 3. With single-use fill-finish assembly, the flow path is self-contained, increasing operator safety and decreasing the risk of contamination.

This transformation was enabled by a roll-up peristaltic pump skid. The addition of that skid and a single-use fill-finish assembly greatly increased the use and flexibility of the company’s filling line both for the H1N1 flu vaccine and for new drug forms in the future (Figure 3).

Implementation of this single-use final filling solution increased capacity by 40% and reduced filling time by one-third.

Additionally, this single-use fill-finish system increases the flexibility of manufacturing, even for facilities where an existing system must be retrofitted. The added flexibility afforded by disposables is applicable to both single and multi-product filling operations, which can be run in simultaneous campaigns using the same hardware.

Following the H1N1 pandemic, single-use technologies continued to be integrated into vaccine manufacturing processes. This approach was paramount during the 2014 Ebola outbreak, where extensive adoption of single-use processing vessels and assemblies were essential to expedite clinical material production.

2. Expansion of Single-Use Across the Vaccine Manufacturing Workflow

In response to the need for accelerated clinical production of vaccines, rapid, scalable, and GMP-compliant processes were needed to respond to Ebola, MERS and Zika outbreaks in 2014-2015.

Rather than use the actual virus in a modified form in the vaccine, several manufacturers developed vectors, virus-like particles or nucleic acid platforms, to carry the antigen rather than use the actual virus in a modified form in the vaccine. The goal was to establish a templated vaccine manufacturing process rather than reinventing the process for every target. For Ebola, MERS or Zika vaccine, viral vectors were the modality of choice and included adenovirus, vesicular stomatitis virus (VSV) or measles.

During this period, our collaboration with the Jenner Institute at Oxford University focused on transitioning labor- and time-intensive adenovirus-based vaccine process development to a platform utilizing single-use technologies and novel purification techniques.

Using a Rabies vaccine candidate, the platform delivered a target of 2000 doses from a 4 L batch for Phase 1 clinical studies with a process efficiency of approximately 50 %.

The resulting flexible, single-use template is a more affordable platform for subsequent vaccine production. Other adenovirus serotypes were tested to validate the platform approach in order to accelerate vaccine development and manufacturing. The Jenner Institute has leveraged this same approach in response to the Covid-19 pandemic, demonstrating a process development time of two months versus the typical one-year timeframe (Figure 4).

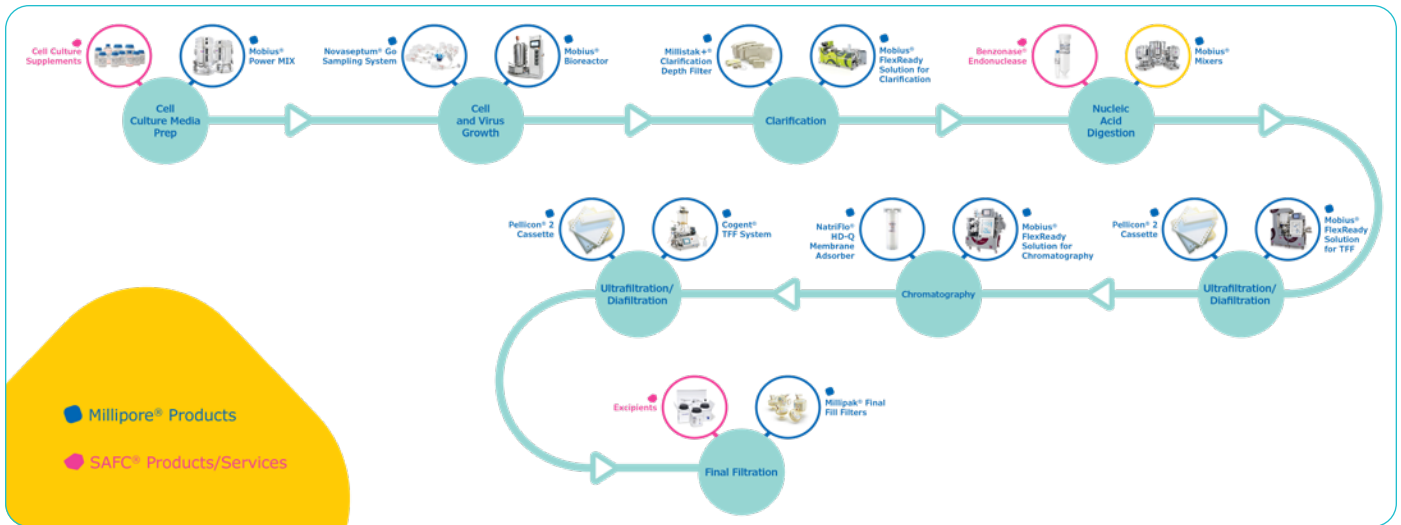


Figure 4. Illustration of a generic adenovirus-based vaccine process with single-use technologies

3. Expanding the Benefits of Single-Use via Outsourcing

Vaccine manufacturing can also be accelerated by outsourcing production and validation of customized single-use assemblies to a supplier with extensive experience and inventory. The advantages of outsourcing single-use assemblies include quality release to speed manufacturing, higher quality assurance and standardized quality, all of which reduce risks in an emergency.

Outsourcing process development and manufacturing to a C(D)MO can provide a short-term increase in capacity and speed while internal facilities are prepared. This approach was ramped up during the H1N1 influenza pandemic and intensified to face the Covid-19 pandemic. Despite this, current capacities are still limited and coordination with various sites that use different technologies is not without challenges.

4. Toward More Flexible Manufacturing of Vaccines

In response to the H1N1 pandemic in 2009, many vaccine manufacturers invested in expanding existing facilities and in new facilities. While this created significant capacity for a particular vaccine, these facilities might not be sufficiently flexible for production of other vaccines, such as that for Covid-19.

With a global surge in demand for new and various vaccines, the establishment of new flexible manufacturing facilities is a viable option; this is an approach that has been already established in the veterinary vaccine industry. There are numerous considerations when establishing a new facility including financial impacts of manufacturing options, forecasting and capacity, technical evaluation of existing or new manufacturing sites and time-to-market.

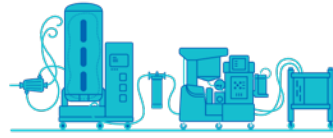
Ultimately, a facility should have the flexibility to scale up or down depending on demand and support different platforms whether it be a viral vector, proteins, live attenuated virus or mRNA. With enormous time pressures and many competitors in the vaccine space, what is the best way to rapidly deploy flexible manufacturing facilities?

A manufacturing facility fully equipped with single use provides advantages in all of the above areas, including decreased overall expenditure, time and footprint, as well as accelerated production and increased flexibility (Figure 5). Facility construction time is also significantly reduced.

Traditional large vaccine manufacturing facilities



Manufacturing facility using single-use technologies



	Traditional stainless facility	Single-use facility
Capex required	~\$500M to \$1B	\$20-100M
Time to construct	5-10 years	1.5 years
Change over time	4 weeks	0.5 days
Footprint	~>70,000 m ²	~11,000 m ²

Advantages of Single-Use Platforms

- Reduces capital
- Easy to use
- Reduces cross-contamination risk
- Faster production
- Reduces cleaning costs
- Flexibility to change scale or process
- Reduces time to market

Figure 5. Advantages of a manufacturing facility equipped with single-use technologies versus traditional large vaccine manufacturing plants.

5. Preparing for Disease X

Disease X is listed on the “R&D blueprint of priority diseases” published by the WHO. This ominous name represents a hypothetical, unknown pathogen that could cause a future epidemic. No doubt, more outbreaks and pandemics will happen in the future, and may be either a recurrence of a known foe or an emerging virus. Fortunately, the lessons learned from previous challenges are firmly embedded in the biopharmaceutical industry and enable vaccine developers, manufacturers and suppliers to respond in an increasingly effective and timely manner.

Our collective response to the next outbreak will incorporate new platforms and collaborations, rely on robust supply chains and leverage flexible and manufacturing facilities, able to quickly meet the surge in demand for a vaccine.

- Plotkin, S. et al., The complexity and cost of vaccine manufacturing. *Vaccine*. (2017) 35:4064-4071.
- Loftus, P and Walker, J. Drugmakers prepare to make Coronavirus treatments. *Wall Street Journal*. April 23, 2020.
- Fedosyuk et al, *Vaccine*. 2019
- [Enabling Solutions for Vaccines and Viral Therapies](#)

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