Biotech

White Paper

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Flexible Platform Solutions Overcome Vaccine Production Challenges

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1 Introduction

Vaccines have been used since Edward Jenner first experimented with smallpox in the 1790s and have evolved significantly in modern times. Today, vaccines have a diversity of antigens and targets, and with advances in drug manufacturing there is a huge variety of development and administration formats.

The team from Pall Biotech explores the challenges of vaccine development and how they can be overcome by applying a quality by design (QbD) platform approach from early process development phases forward. The impact of the COVID-19 pandemic on vaccine production is evaluated, with insight on how flexible, integrated, closed-system processing is advancing the future of safe and efficacious vaccine production.

2 Process-Based Challenges

In modern drug development, it is common to hear that “the product is the process”. This is said so often because regardless of the product, there is little hope for success in drug development without a clearly defined and documented process that will scale from clinical to commercial production phases, while meeting or exceeding regulatory guidelines.

The unique situation with vaccine production is that each class of vaccine presents specific process development and manufacturing challenges, and the scale of production varies depending upon the targeted disease population. To overcome these challenges, manufacturers must rigorously characterize the manufacturing process.

3 The Case of COVID-19

Traditionally, vaccines can take five years or more to research and develop. However, there has been a tipping point with COVID-19, where process development and manufacturing timelines have been accelerated to be shorter than ever. The intense focus on the pandemic across the globe has led to a parallel approach to innovation with 145 vaccine candidates being introduced as of August 2020. At least 30 candidates are already in clinical trials, barely six months after the discovery of the disease[i].

However, this is not an industry that re-invents the wheel overnight. A great deal of this work has drawn on past successes and failures as a reference point or building block. And because the industry is so highly regulated, safety and efficacy will remain paramount in testing, even with reduced sample sizes and monitoring times, as clinical trials get underway.

The COVID-19 vaccine candidate mix includes traditional inactivated whole-virus, protein sub-units, and modern viral vector and genetic technologies. Prior knowledge on bioprocessing platforms is being leveraged to get each successful candidate to testing and production phases. In fact, many of the early vaccine candidates have been founded upon platform processes and defined by proven platform unit operations. These platforms are supported by a host of prior knowledge from cell culture for mAb production and relatively recent developments supporting related processes such as viral vector production for gene therapies.

4 Evolution in Real Time

DNA vaccines using plasmid DNA (such as Inovio's INO-4800) and recombinant viral vector processes (such as those used by Jenner Institute's ChAdOx1) are two platform processes that have previously been used for vaccine development and production[ii]. Newer processes, such as the use of mRNA and self-amplifying RNA vaccines seem to have great potential but have never been approved. Because of the novel nature of these vaccines, it can be expected that they may take longer through clinical trials than those using proven methods. However, with the COVID-19 pandemic in full swing, Moderna was able to reconfigure their platform and bring an mRNA vaccine into clinical trials in July of 2020[iii].

For each of these three examples, a vaccine candidate was designed within hours of receiving the genetic code of the target virus. However, regardless of the formulation of the vaccine, not all will be able to progress at the same speed, and scale-up to meet the billions of doses needed, at least not for this pandemic. Instead, the industry is aiming to bring potential candidates to market, while using this experience as preparation for the next urgent situation. In turn, the industry is evolving in real time when it comes to speed, efficiency and manufacturing capabilities and capacity.

5 Building in Quality

In drug development, a platform can take many forms to support development and manufacturing processes. Even though there is not one single answer for the process of vaccine production, there is one single approach that can benefit all vaccine manufacturers: a platform approach using QbD methodology.

The United States Food & Drug Administration says that a proper QbD approach includes the following elements[iv]:

1. A quality target product profile (QTPP) that identifies the critical quality attributes (CQAs) of the drug product
2. Product design and understanding including identification of critical material attributes (CMAs)
3. Process design and understanding including identification of critical process parameters (CPPs), linking CMAs and CPPs to CQAs
4. A control strategy that includes specifications for the drug substance(s), excipient(s), and drug product as well as controls for each step of the manufacturing process
5. Process capability and continual improvement

The FDA also notes that manufacturers need to leverage prior knowledge where feasible; complete risk assessment, mechanistic models, design of experiments (DoE) and data analysis; and implement process analytical technologies (PAT) throughout.

6 A New Standard of Innovation

For decades, the concept of a platform manufacturing process has been applied to simplify, de-risk and accelerate the development and manufacture of drug substances. Iterative improvements for development and manufacturing, such as the adoption of single-use technology and continuous manufacturing technologies, have brought a new level of flexibility and ease to the industry in the past two decades, but adoption was initially slow. In the past five years the industry has shown a greater willingness to implement platform approaches yet continues to waver on the topic of standardization. The COVID-19 vaccine development rush is helping to put the power of these platform technologies on full display and is acting as a catalyst for the standardization needed to keep innovation moving.

Across the industry, unit operations are being combined into a myriad of final manufacturing environments including traditional facilities, as well as new stick-built and modular, prefabricated formats. The introduction of prefabricated cleanroom concepts offers an end-to-end, total-process solution that looks beyond the core process unit operations and extends to supporting every operation, including buffer preparation and fluid management.

In late 2018, Pall partnered with G-CON Manufacturing♦ to design prefabricated manufacturing suites which can be customized and deployed rapidly to expand manufacturing capacity. These suites feature customizable, pre-configured processing platforms that are scalable and can be repurposed to respond to changing requirements. Implementing this type of prefabricated modular platform means that a vaccine manufacturer can be operational in months versus years for a traditional facility format.

If platform choices are made with a knowledge of both the performance attributes and their benefits in real world processes such as usability, scalability, and economy, time and spend are both optimized. The focus can then be placed on the critical studies needed to adequately characterize performance and get the candidate ready for the next stage in the development process.

7 Partnering for a Better Process

At Pall Biotech, platforms are built and defined based on what the process needs to achieve and at what scale it will ultimately grow to. The Accelerator℠ Process Development Services (PDS) team works with each customer to provide upstream, downstream, and analytical support with platform solutions that scale-up and mature with the process. The process ultimately being the product makes reproducible results that scale a necessity.

For vaccine production with rapid industrialization as the goal, this might mean selecting single-use depth filtration over centrifugation for clarification or using suspension or adherent cell culture systems instead of traditional roller bottle and flatware choices that do not easily scale for viral vector production. Having a range of options and support in building the right platform is critical.

In upstream production, the Allegro™ STR single-use stirred tank bioreactor portfolio leverages decades of bioprocess engineering expertise and has proven to deliver consistent, scalable cell culture performance. Integrated with downstream technologies like the Stax™ mAx single-use clarification platform for depth filtration that can eliminate the need for centrifugation or process additives, vaccine manufacturers can achieve more rapid, robust performance with minimal process

variability. The platform scales directly with a range of formats and sizes suitable for bench-top testing up to large-scale clinical production so the manufacturer has a solution for the life of their process.

Undoubtedly, formulation and filling are a critical part of any drug manufacturing process and demands the highest levels of quality and reliability. Pall has a range of technologies and services that are quality driven and enable end users to carry out their operations with increased reliability and flexibility. The Allegro single-use portfolio features sterilizing grade filters and automated solutions that ensure manual interventions are minimized to increase sterility assurance.

And once technical transfer has been completed, the Pall Scientific and Laboratory Services (SLS) team is available to provide field-based customer and technical support to ensure process quality and reliability. Validation services can also be taken advantage of wherever needed.

8 A Process for the Future

The COVID-19 pandemic has undeniably been challenging, but it has also helped to highlight the importance, and endless potential, of this industry. Process development is being done in a more rapid and focused manner than ever before, truly leveraging the enabling technical platforms and manufacturing models on the market and spurring innovation. If the industry can work this fast for COVID-19, imagine what the future can look like for the next great health challenge, and how this progress can be applied to achieve the same speed with cell and gene, and other breakthrough therapies.

There is no doubt that platform processes, whether from the perspective of a high-level end-to-end process description or limited to established technology choices at the unit operation level, do accelerate, de-risk and ultimately deliver the results required. The journey may be complex, but it can be simplified and accelerated with help from the right partners who reinforce these platforms with standardized, robust and versatile products, and prior knowledge of how to integrate, implement and optimize total-process solutions.

9 References

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