How to Speed Up Vaccine Development and Production with Genetic Vaccine Technology

Recipharm

The COVID-19 pandemic has been challenging and disruptive for societies globally, forcing us to adapt ways of working and living to safeguard vulnerable people from infection. The outbreak has also fostered creativity and innovation when it comes to adapting to change, particularly in the pharmaceutical and healthcare spaces as we have sought out treatments and care approaches to save lives.

Among the most important of these innovations was the development of a number of effective vaccines. These vaccines were developed, commercialised and delivered with remarkable and unprecedented speed, kick-starting the largest mass-vaccination campaign in history.

The secret to this incredible achievement is two-fold. It is a combination of existing work on coronaviruses, following previous SARS and MERS epidemics – caused by viruses related to the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) that causes COVID-19 – and the harnessing of new technology, such as genetic vaccines (mRNA).

The technology behind genetic vaccines differs from that of traditional vaccine technology. Traditional vaccines are usually developed by using an attenuated or inactive version of that virus. A genetic vaccine works slightly differently – rather than injecting a weakened form of the virus into the body, these vaccines use part of the virus's own genes to stimulate the creation of its proteins by cells in the body, which then stimulate an immune response.

It is this difference that makes genetic vaccines such an exciting new frontier. In this eBook, we will explore why the unique attributes of genetic vaccines makes them such an important tool not just in the global recovery from COVID-19, but in the fight against future pandemics as well.

We will explore the challenges and pitfalls in developing new genetic vaccines, and in manufacturing them following approval. In addition, we will discuss how strategic partnerships with expert contract development and manufacturing organisations (CDMOs) can support vaccine developers to bring their innovations to market.

UNDERSTANDING GENETIC VACCINES

A range of possible technologies can be used to create a vaccine. Traditional approaches involve the use of attenuated or inactivated viruses (or other pathogens, such as bacteria), designed to reduce the risk of illness while stimulating an immune response.

A few examples of traditional processes include:

Attenuation as a process entails the cultivation of active viruses under conditions that disable their virulent properties. Alternatively, a closely related virus that is less dangerous may be used. This approach can provoke more durable immunological responses, but such vaccines are not safe for use in immunocompromised individuals, and on rare occasions mutate to a virulent form and cause disease.

Inactivation involves the use of previously virulent micro-organisms that have been destroyed with chemicals, heat, or radiation – "ghosts", with intact but empty bacterial cell envelopes.

Toxoid vaccines contain inactivated toxic compounds that cause illness rather than the micro-organism.

A subunit vaccine uses a fragment of a virus to create an immune response.

This is not an exhaustive list, and other approaches are also commonly used.

Genetic vaccines are different. Instead of injecting the body with the pathogen – or fragments of the pathogen – to promote an immune response, genetic vaccines work by delivering one or more genes that encode proteins of the pathogen to stimulate the immune system.

There are several possible approaches that can be taken when developing genetic vaccines:

mRNA Vaccines

Messenger RNA (mRNA) vaccines use a synthetic RNA copy of a virus' messenger RNA (mRNA) to produce an immune response. The vaccine transfects the modified mRNA into immunity cells, which then instructs the cells to build foreign protein that would normally be produced by the pathogen.

These protein molecules then stimulate an adaptive immune response, which teaches the body to identify and destroy the corresponding pathogen or cancer cells. The mRNA is delivered by a co formulation of the RNA into lipid nanoparticles which protect the RNA strands and help their absorption into the cells.

DNA Vaccines

A DNA vaccine works in a similar way to mRNA vaccines. However, rather than using RNA, it transfects a specific antigen-coding DNA sequence onto a patient's cells. DNA vaccines inject genetically engineered plasmid containing the DNA sequence encoding the antigen against which an immune response is sought. The infected cell then produces the antigen, thus causing a protective immunological response.

A History of Genetic Vaccines

The two COVID-19 vaccines developed by Pfizer and BioNTech, and by Moderna, were developed using the mRNA approach.

The Pfizer vaccine is the first such vaccine to be approved for widespread use by the US Food and Drug Administration (FDA), the EU's European Medicines Agency (EMA), and other national regulatory bodies, such as the UK's Medicines and Healthcare products Regulatory Agency (MHRA).

However, the genetic vaccine approach is not new. The first mRNA vaccines were initially developed in the early 1990s in an effort to design an approach that could allow the rapid creation of safe and effective vaccines in a pandemic situation.

In recent decades, mRNA vaccines have been studied for diseases including:

- Rabies
- Zika
- Cytomegalovirus (CMV)

In addition, a large-scale influenza trial was carried out in humans from 1993–1996,[1] although currently used influenza vaccines use traditional inactivated, recombinant or attenuated platforms.

DNA vaccines have been explored for a number of decades, too. Several DNA-based vaccines have been approved by both the US FDA and the US Department of Agriculture (USDA) for veterinary use. These include:

- a vaccine against West Nile Virus in horses
- a melanoma vaccine for dogs

In addition, there are several human clinical trials on DNA vaccines in progress. The U.S. National Library of Medicine records more than 160 different DNA vaccines currently being tested in human clinical trials.[2] Of these, 62% trials are devoted to cancer vaccines and 33% are against human immunodeficiency virus (HIV).

Several viral vector vaccines which, like DNA vaccines, carry DNA into a host cell, have also been approved for use. The Janssen Ebola vaccine, for example, was approved by the European Commission in 2020. It uses the company's AdVac® viral vector technology to prompt an immune response.[3]

Advantages Over Standard Approaches

While still in their infancy, relatively speaking, genetic vaccines offer considerable benefits compared with other approaches that make them a highly attractive alternative for vaccine development:

Adaptability: the underlying technology behind mRNA vaccines is highly flexible and adaptable. This means that it can be used to develop vaccines for a wide array of pathogens. It also allows for rapid updates to existing and approved mRNA vaccines as new viral mutations (variants) evolve or whole new viruses are discovered. As mRNA vaccines are based on sequences of viral proteins, making a new vaccine could simply involve changing the mRNA sequence to reflect the genetic code of the new variant.

Cost-effectiveness and resource efficiency: due to the adaptability of the platform, genetic vaccines (and mRNA vaccines in particular) are quicker to develop and manufacture than traditional vaccines.

For inactivated or attenuated virus vaccine platforms, the design, development and manufacturing process can take months or years. The manufacturing of a sufficient quantity of viruses to produce enough vaccine to inoculate a large population can be particularly cumbersome and require facilities that are designed to handle products with elevated biosafety levels. While these approaches are used to drive mass vaccination campaigns, such as seasonal influenza, they are not particularly efficient when it comes to delivering the kind of campaign needed to tackle a pandemic.

In contrast, mRNA vaccine development can be compressed into a matter of weeks. The Moderna COVID-19 vaccine development process – from vaccine design to manufacturing to shipment – took just seven weeks. This excludes the trial and testing timeline, which necessarily takes the same amount of time as it does with traditional vaccine technologies to ensure safety.

There are some disadvantages to genetic vaccines. For example, as they only allow a fragment of the pathogen to be made, they often produce a weaker protective immune response compared with attenuated virus technologies. Some also pose stability and storage challenges in contrast to other approaches, which reduce their shelf life.

However, solutions to these issues are being worked on. Moreover, the benefits of genetic vaccines with regards to speeding up the development and manufacturing process go a long way towards addressing any disadvantages. New boosters can be developed quickly to overcome poor immune responses, and additional batches can be manufactured rapidly to replace expired units.

TACKLING DEVELOPMENT CHALLENGES

With all of this in mind, it is no surprise that genetic vaccines are dominating the virotherapy agenda. Nevertheless, while offering considerable benefits to developers in creating effective new products for preventing infections or even fighting cancers, the development and manufacturing of genetic vaccines pose challenges for pharma companies. Failure to address them could delay or prevent the successful commercialisation of a new product.

Development Issues

Common development pitfalls that need to be overcome include:

Novelty of the technology: the small number of established approved genetic vaccines in widespread use either among human patients or animals means that there are few platforms or production processes for developing promising and scalable vaccine candidates quickly. This means that, for pharmaceutical companies exploring potential genetic vaccines for the first time, they have no existing approaches to use as a template to plan their own project, and therefore must design their own processes themselves.

Bringing vaccines to trial: Very few therapies – whether for vaccines or other treatments – make it to clinical trial.

As an approach that is still at the cutting-edge of medical technology, genetic vaccines require considerable discovery and development work compared with traditional methods, which benefit from established understanding of how they work. This is crucial to ensure their viability and their safety for human test subjects.

Navigating regulatory approval: The novelty of genetic viruses means that regulators require considerable evidence garnered from unimpeachably performed trials before they will give approval. This is the case even for emergency use, as we have seen with COVID-19 vaccines. There are no established development pathways to speed approval, so every step of the approval process must be followed.

Manufacturing Barriers

In addition to development issues that must be addressed, there are obstacles at the manufacturing stage that need to be overcome to ensure successful commercialisation and delivery:

Dedicated manufacturing capacity: with genetic vaccines – and particularly DNA vaccines – still in their infancy, there are few pharma companies that have the capability, infrastructure and manufacturing capacity to deliver the vaccines efficiently and reliably. Many will need outside support from the limited number of partners with experience in this specialist area. Issues sourcing raw materials: again, with experience in genetic vaccines at a premium, it is a challenge for many pharma companies to find suppliers with the experience to provide the specialist raw materials in a sustainable and secure supply.

Transport and storage challenges: the nature of genetic vaccines means that they pose stability issues, requiring cold storage as low as -70° C. This poses challenges when it comes to transporting such vaccines to healthcare providers (HCPs) and to endpatients, particularly in emerging economies where the cold-chain logistical infrastructure may not exist. The short shelf life of genetic vaccines means that – in the event of a mass vaccination programme for a future pandemic – pharma companies must be able to manufacture and deliver new batches to where they are needed quickly and efficiently.

HOW OBSTACLES CAN BE OVERCOME

While these are significant challenges, they needn't hinder genetic vaccine development success. With the support of expert contract development and manufacturing organisation (CDMO) partners that specialise in supporting the development of genetic vaccines, pharma companies can be confident they have the experienced help they need to deliver their discovery to market.

CDMOs Can Help

Many CDMOs already specialise in specific manufacturing technologies that are already harnessed in traditional vaccine development and can also support in genetic vaccine development and manufacturing.

From aseptic filling to lyophilisation to extend the shelf life of vaccines and other pharmaceutical products, CDMOs have the dedicated infrastructure in place to support pharma companies in streamlining the development process for their new genetic vaccines.

Moreover, the expert teams employed by CDMOs have the experience and creativity to design and develop new processes for their existing manufacturing lines. They can leverage their experience from other, non-genetic vaccine projects, in general production issues, such as labelling, and apply it to developing new ways of working that fit the needs of genetic vaccine development and manufacturing. This can allow them to deliver specialist novel technologies, such as genetic vaccines, without the need to invest substantially in new equipment.

CDMOs can use their own supply networks to explore new sources for materials with long delivery times, such as vials. They can even offer customers the use of their own stock of materials to start production, when needed.

In addition, CDMOs can also use their knowledge of topics beyond manufacturing, such as cold-chain transport, global regulations and global shipping, to advise companies on navigating the approvals process and the complex global market.

Benefiting from Expert Help

Working with such partners, pharma companies can be confident they can embark on developing their discovery straight away, without having to invest in building new production facilities or lines from the ground up.

They can also benefit from the expert guidance and support they need to design and plan their projects to deliver a successful and commercially viable product in the shortest possible time frame.

HOW RECIPHARM CAN HELP

Recipharm's experience, global footprint and array of specialist infrastructure makes it well placed to support pharma companies with their future genetic vaccine development and manufacturing needs.

A leading CDMO, Recipharm operates development and manufacturing facilities across the globe, making it an ideal partner for pharma companies seeking to deliver genetic vaccines internationally.

Our 9,000 strong team includes experts in delivering cutting-edge vaccine projects – using traditional approaches and genetic methods. They are focused on supporting pharmaceutical companies in taking new genetic vaccines from early development through to commercial production.

Our locations include:

- Portugal
- Spain
- Sweden
- UK
- US
- France
- Germany
- India
- Israel
- Italy

In addition, Recipharm uses its infrastructure and its people's talents to offer full analytical service for release and stability testing. The company's existing infrastructure allows it to extend its offered services to the formulation of the bulk vaccine product.

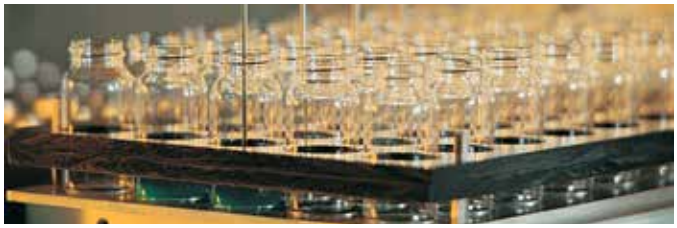
Its regulatory intelligence supports the customer in regulatory activities, accelerating and streamlining the filing process.

As a result, Recipharm can offer a full manufacturing and analytical service package starting with the pure mRNA and ending with the packaged vaccine products. Recipharm's Quality Persons (QPs) are qualified to certify vaccines for the EU market.

Recipharm in Action

A pharmaceutical company developing a new genetic vaccine for clinical trial recently approached Recipharm to support in creating an effective lyophilisation cycle for their product that could save time and streamline manufacturing. This was crucial to maximise production line efficiency while also enhancing the stability and shelf life of the finished vaccine.

Following comprehensive study analysis and other processes, Recipharm's experts identified a solution to shorten the lyophilisation cycle timeline by 30%. This effectively



accelerated production speeds for the vaccine, reducing throughput time, enlarging production capacity and reducing costs.

Recipharm's procurement specialists were also able to source raw materials, including glass vials for primary packaging within a lead time of just three months, at a time when such packaging was in short supply globally.

Our efficient and diverse supply network also minimised the risk of delays to the customer's project, enabling it to be delivered globally on time.

THE FUTURE OF VACCINE DEVELOPMENT

The COVID-19 pandemic has shown the world the value of genetic vaccines in delivering effective protection against serious disease. Both DNA and mRNA vaccines are highly promising fields, so it is no surprise that they are evolving quickly.

To take advantage of this exciting technology, developers need expert support in navigating the challenges inherent in the development process.

By working with expert partners, like Recipharm, developers can be confident they have the support and insight they need to deliver successful and effective genetic vaccines to market, transforming healthcare in the future.

To find out more about how Recipharm can support you on your vaccine development journey, contact us today.

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Recipharm is a leading global pharmaceutical Contract Development and Manufacturing Organisation (CDMO). We provide pharmaceutical companies around the world with tailor-made development and manufacturing services, including a wide variety of drug dosage forms, and inhalation products and devices.