



Upholding biosafety standards despite the acute need for a SARS-CoV-2 vaccine



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Viral vaccines were the first pharmaceuticals manufactured using living cells, revolutionizing the industry at a time when regulatory compliance was controlled by the local pharmacopoeias (United States, European or Japanese). More recently the World Health Organization created global guidelines which are used alongside the Pharmacopoeia to deliver alignment. Such traditional viral vaccines, although widely used and effective, have a significant downside when creating a product for a new agent: they take a long time to evolve, test in clinical trials, and scale up for mass delivery. Advances in vaccine technology has progressed to enable several novel strategies to be employed which reduces the traditional steps needed for vaccine development and production. Pseudo-typed virus vectors, virus-like particles or DNA or RNA as a vaccine have all been developed and are about to enter clinical trials against SARS-CoV-2. Although they possess little in the way of pedigree in the vaccine space, such products do have shorter development, manufacturing, and scale up times—huge benefits in the light of the current COVID-19 challenge. Being sourced from recombinant DNA technology, they are regulated under biologics guidelines. These place many different points of emphasis compared with the traditional vaccine guidelines of the pharmacopoeias.

Issues and obstacles remain

Despite the progress in recent times there are several factors that have been hindering the path towards new and better vaccines. Lack of funding to cover the significant costs is certainly one. In cases where the agent is novel, such as in the case of SARS-CoV-2, there is little immunological information

available on what constitutes protective immunity in individuals who have recovered from a natural infection. This calls for wider population data to be collected and analyzed from a number of geographies and age groups. In general, there is a need to better understand the protective correlates of immunity across the population. Efforts to make effective candidate vaccines against other Human Coronaviruses have had in the past poor success. A model animal with a more similar immune system to that of human beings could also make a big difference.

As vaccines are used on healthy individuals, and often on children and the elderly, the highest vigilance in ensuring a safe and effective product must be taken. As early as for pre-clinical testing, it is vital to ensure the vaccine candidate's quality and efficacy. To this end, current GMP guidelines cover three main task areas to consider when manufacturing a vaccine: ensuring the quality of the starting material, controlling the manufacturing process, and testing the vaccine product.

Scrutinizing the source

Sourcing a vaccine's starting materials must be considered carefully and with attention to the Good Manufacturing Practices (GMP) guidelines. If, for example, a viral seed is used for production, the provenance of the virus must be presented along with a complete characterization including the virus's entire genome sequence. Following characterization, the next issue to be addressed is safety. Viral vaccine seeds have several potential sources of contamination: the person or animal from which the virus was isolated, the cells used for production, other raw materials used for isolation and attenuation and the



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materials used in the banking and propagation of cells for growth of the viral seed (e.g. serum). The starting materials are characterized through tests and suppliers must also certify to have performed the appropriate audits.

It is important to establish a validated manufacturing process to ensure that the conditions are reproducible between production batches. If recombinant technology is involved, the molecular integrity of the gene being expressed and the phenotypic and genotypic characteristics of the host cell after long-term cultivation (i.e., end of production testing) should be established.

In addition to in-process controls, a considerable number of quality control (QC) tests to rigorously analyze the active substance and the final product must be performed. As most vaccines are administered as injectables, sterility testing as well as bioburden and endotoxin testing are pivotal to ensure a vaccine's safety. Further tests on the final product are conducted to determine identity, purity, and the potency to bring about immune protection. The analyses typically include particle counting, serine protease activity, total protein content, mycoplasmas, extractable volume, pH, osmolarity and visual product inspection. With time-to-result becoming ever more important, it is worth noting that many QC tests (e.g., sterility, bioburden) can be vastly accelerated and streamlined when using rapid or automated methods.

The race is on

Globally, over 200 research groups and pharmaceutical companies are currently competing to develop a vaccine against this novel coronavirus. Amongst the current frontrunners there are several vaccine candidates based on RNA already in the clinic. It is mooted that this approach could more easily yield vaccines that prompt the expression of multiple conserved antigens, with no need for formulation updates when genetic variants of the virus appear. However, an RNA-based vaccine has never before been approved on a large scale for use in humans as a viral vaccine so these products do carry a higher degree of risk. Alongside the RNA vaccines there are several recombinant adenoviral vaccine candidates expressing SARS-CoV-2 spike proteins which have already initiated clinical trials. These recombinant species are relatively fast to create and have allowed some to be early to the clinic for vaccine studies. Manufacturers have been building new facilities and scaling up the production process alongside the clinical trials process to reduce the time taken to bring large scale production online. However, no shortcut will be possible. Patient safety comes first, whatever the strategy.

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