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Biopharmaceutical Innovations and a race for Human Vaccines

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Abstract

Biotechnology is the technological application of biological organisms, systems, and processes to develop, make, or modify products for specific uses such as pharmaceuticals, crops, and livestock. Traditional methods are the employment of artificial selection and hybridization, but modern usage also includes genetic engineering as well as cell and tissue culture technologies. In this research, we review some biotechnologies applied for the development and production of vaccines especially in respect of coronavirus. The immune response generated and efficacy rate achieved by these vaccine jabs of eminent biotechnology company is critically analysed. In light of the WHO specified vaccine approaches, viral vector vaccines and mRNA technology have received first time such wide approval in clinical trials and marketability. The regulatory mechanism globally and domestically has different implications to it. The biotechnology law being governed by the Drugs and Cosmetics Act 1940 and Rules 1945 in respect of new drug which also includes a new vaccine employing mRNA technology is observed together with the Clinical Trial Rules. Where on one hand without FDA approvals, WHO Emergency Listing has given place to vaccines like Pfizer, Jansen and Moderna; on the other hand, CDSCO and Clinical Trial Rules have given green signals to Covaxin and Covishield fast tracking the process to bring impactful vaccine in dire need. The world has received vaccines on a time-limited basis and based on a risk-versus-benefit evaluation defying the traditional time lagging process. The vaccination drive has become the flagship achievement of modern biotechnology which is immunizing billions of populations till the time we achieve the herd immunity and slow down the spread to zero.

Keywords: Biotechnology; Vaccine; Viral Vector; Drugs; FDA; WHO; Immunity

Introduction

That's the guiding principle of Serum Institute of India, India's No. 1 Biotech Company and the World's Largest Vaccine Manufacturer (by volume, more than 1.3 billion doses) which includes Polio vaccine.

The ability to secure property interests in technological processes, products and know-how encourages the development of technology. One factor to evaluate the competitiveness in biotechnology is the effectiveness of intellectual property law. Biotechnology gives rise to a vast array of new inventions. The inventions may be placed into two categories: products and processes. Products include organisms, such as genetically modified micro-organisms, cell lines, plants and possibly even animals. Finally, there are products of organisms, such as drugs, chemicals, monoclonal antibodies. Processes include various ways to make new organisms or to use an organism to make some product [1].

Biotechnology focuses on the industrial use of recombinant DNA, cell fusion, and novel bioprocessing techniques. These techniques will find applications across many industrial sectors including pharmaceuticals, plant and animal agriculture, specialty chemicals and food additives, environmental applications, commodity chemicals and energy production and bioelectronics. Competitive advantage in areas related to biotechnology depends as much on developments in bioprocess engineering as on innovations in genetics, immunology, and other areas of basic science [2].

Vaccination is the deliberate immunization of an organism against infection by a disease agent. It can also mean the immunization of a person against any agent capable of provoking an immune response. The agent provoking the response can be an infectious organism, but it can also be a medium-sized molecule (i.e., a protein toxin) or part of a protein from one's own body (e.g., stimulating an immune response to a tumor). Anticipated advances in cell biology, immunology, molecular genetics, genomics, and cellular immunity will greatly accelerate the production of cheap, safe, effective vaccines.

Vaccination is perhaps the most effective means of controlling infectious diseases. It has been mainly responsible for the eradication of smallpox and for the control of yellow fever, poliomyelitis and German measles in the human population, and of Newcastle disease, foot-and-mouth disease and Marek's disease in domestic animals [3].

History of Vaccination

The history of vaccination dates back to the 1798 studies by Edward Jenner, an English physician who used cowpox virus to immunize people against smallpox. Almost 200 years later, the comprehensive smallpox vaccination program established by the World Health Organization eventually led to the worldwide eradication of that disease. That success story is proof of the

tremendous potential of vaccination and has led to the development of vaccines against almost all infectious agents affecting people and animals. The ultimate objective of vaccination is to induce an immune response that subsequently recognizes the infectious agent and fights off the disease. Vaccination usually is accomplished with either weakened or attenuated live agents; with inactivated agents that no longer can cause disease; or with selected, immunogenic parts of the disease agent called subunit vaccines [4].

Traditional methods of creating vaccines include using a similar agent that does not cause disease, such as Jenner's cowpox virus, or passing a pathogenic disease agent through a laboratory host system to weaken or attenuate the agent. Inactivating the disease agent with one or more chemicals also can be used to create vaccines. In addition, extracting, purifying, and using one or more parts of the disease agent can be used to induce a protective immune response. An immune response is stimulated when a foreign substance called an antigen is encountered by the immune system. The animal's immune system has the ability to distinguish between a foreign substance, such as the proteins in a virus or bacterium, and its own proteins. It does not matter whether the foreign proteins are from a disease agent or a vaccine against the disease agent, the immune response is similar: when the animal encounters the virus or bacteria again, the immune system recognizes it and, ideally, responds to protect the animal from the disease.

Although vaccination has saved countless lives, it can have both favourable and unfavourable consequences. Certain vaccines—specifically, live vaccines—can revert back to pathogenic organisms and produce disease or, in some instances, even death. The development of rDNA technologies has provided new ways of attenuating disease agents by modifying their genetic makeup, or genomes, to create safer, more efficacious vaccines [5].

Vaccines prepare the immune system to recognize and attack invaders or antigens. Once an organism has been vaccinated, it becomes immune because it contains populations of cells carrying molecules on their surfaces that recognize particular antigen molecules produced by, or part of, an infectious agent. Antigens are frequently, but not always, proteins encoded by the genome of the infectious agent; they can also be other molecules, such as complex carbohydrates [6].

Types of Vaccine Technologies

There are four main approaches to designing a vaccine: Whole Pathogen Vaccine Approach, The Viral Vector Approach, The Subunit Approach and The Genetic Approach. Their differences lie in whether they use a whole virus or bacterium; just the parts of the germ that triggers the immune system; or just the genetic material that provides the instructions for making specific proteins and not the whole virus. According to World Health Organisation (WHO) and United States National Institute of Allergy and Infectious Diseases (NIAID), the below mentioned types of vaccines are delved into for getting a clearer picture on its functioning approach.

- Whole Pathogen Vaccine Approach employs Inactivated Vaccine and Live Attenuated Vaccines. The first way-Inactivated Vaccine is to take the disease-carrying virus or bacterium, or one very similar to it, and inactivate or kill it using chemicals, heat or radiation. This approach uses technology that's been proven to work in people – this is the way the flu and polio vaccines are made – and vaccines can be manufactured on a reasonable scale. A live-attenuated vaccine uses a living but weakened version of the virus or one that's very similar. The measles, mumps and rubella (MMR) vaccine and the chickenpox and shingles vaccine are examples of this type of vaccine.
- The Viral Vector Approach employs Viral vector vaccine. This type of vaccine uses a safe virus to deliver specific sub-parts – called proteins – of the germ of interest so that it can trigger an immune response without causing disease. To do this, the instructions for making particular parts of the pathogen of interest is inserted into a safe virus. The safe virus then serves as a platform or vector to deliver the protein into the body. The protein triggers the immune response. The Ebola vaccine is a viral vector vaccine and this type can be developed rapidly.
- The subunit approach employs a subunit vaccine. It's the one that only uses the very specific parts (the subunits) of a virus or bacterium that the immune system needs to recognize. It doesn't contain the whole microbe or use a safe virus as a vector. The subunits may be proteins or sugars. Most of the vaccines on the childhood schedule are subunit vaccines, protecting people from diseases such as whooping cough, tetanus, diphtheria and meningococcal meningitis.
- The genetic approach employs the Nucleic acid vaccine. Unlike vaccine approaches that use either a weakened or dead whole microbe or parts of one, a nucleic acid vaccine just uses a section of genetic material that provides the instructions for specific proteins, not the whole microbe. DNA and RNA are the instructions our cells use to make proteins. In our cells, DNA is first turned into messenger RNA, which is then used as the blueprint to make specific proteins. A nucleic acid vaccine delivers a specific set of instructions to our cells, either as DNA or mRNA, for them to make the specific protein that we want our immune system to recognize and respond to. Because of the pandemic, research in this area has progressed very fast and some mRNA vaccines for COVID-19 are getting emergency use authorization, which means they can now be given to people beyond using them only in clinical trials.

Coronaviruses and Vaccine Approval Mechanism

There are hundreds of coronaviruses, most of which circulate among such animals as pigs, camels, bats and cats. Sometimes those viruses jump to humans—called a spill over event—and can cause disease. Four of the seven known coronaviruses that sicken people cause only mild to moderate disease. Three can cause more serious, even fatal, disease. SARS coronavirus (SARS-CoV) emerged in November 2002 and caused severe acute respiratory syndrome (SARS). That virus disappeared by 2004. Middle East respiratory syndrome (MERS) is caused by the MERS coronavirus (MERS-CoV). Transmitted from an animal reservoir

in camels, MERS was identified in September 2012 and continues to cause sporadic and localized outbreaks. The third novel coronavirus to emerge in this century is called SARS-CoV-2. It causes coronavirus disease 2019 (COVID-19), which emerged from China in December 2019 and was declared a global pandemic by the World Health Organization on March 11, 2020.

Once a vaccine has reached pre-approval stage following clinical trials, it is assessed by the relevant regulatory body for compliance with quality, safety and efficacy criteria. Following regulatory approval, manufacturers can submit a vaccine to WHO for prequalification (PQ), an assessment process that ensures quality, safety and efficacy and helps the UN and other international procurement organizations determine the programmatic suitability of a vaccine.

During global health emergencies, the WHO Emergency Use Listing Procedure (EUL) may be used to allow emergency use of the vaccine. The EUL exists because, in a pandemic situation, products that could benefit the lives of people all over the world may be prevented from coming to market with sufficient speed. The EUL is a fast-tracked but rigorous process, designed to bring impactful products to all those in need, as quickly as possible, on a time-limited basis and based on a risk-versus-benefit evaluation. The WHO PQ/EUL recommendation may be used by UN agencies such as UNICEF and the Pan American Health Organization Revolving Fund for procurement decisions in low- and middle-income countries. Gavi also relies on WHO EUL/PQ to specify which vaccines its funds may be used to purchase.

Analysis of Covid Vaccines and Efficacy

- The Pfizer Vaccine uses the mRNA technology which has been under development for years but this is the first time mRNA has been cleared for use in humans. The mRNA based covid vaccine works by taking the body to produce a harmless each of the virus triggering an immune response. It is said to be easier to produce over traditional vaccines which generally use a dead virus or weakened virus to produce an immune response. Analysis of the data indicates a vaccine efficacy rate of 95% ($p<0.0001$) in participants without prior SARS-CoV-2 infection (first primary objective) and also in participants with and without prior SARS-CoV-2 infection (second primary objective), in each case measured from 7 days after the second dose.
- The Moderna Covid-19 Vaccine also uses mRNA technology, like all vaccines, those vaccinated gain protection without ever having to risk the serious consequences of getting sick with COVID-19. Interim findings from this clinical trial, using data from participants with a median of 2 months of follow-up, indicate that the Moderna COVID-19 vaccine efficacy after 2 doses was 94.1% (95% confidence interval = 89.3%–96.8%) in preventing symptomatic, laboratory-confirmed COVID-19 among persons across age, sex, race, and ethnicity categories and among persons with underlying medical conditions.
- Johnson & Johnson's Janssen (J&J/Janssen) COVID-19 Vaccine uses the Viral Vector Technology which uses a safe virus that serves as a platform or vector to deliver the protein which in turn triggers the immune response. The J&J/Janssen vaccine was 66.3% effective in clinical trials (efficacy) at preventing laboratory-confirmed COVID-19 illness in people who had no evidence of prior infection 2 weeks after receiving the vaccine. People had the most protection 2 weeks after getting vaccinated.
- Bharat Biotech COVID-19 Vaccine (COVAXIN) is developed with Whole-Virion Inactivated Vero Cell-derived technology. They contain inactivated viruses, which cannot infect a person but still can teach the immune system to prepare a defence mechanism against the active virus. It has shown the efficacy of 78 per cent in the second interim analysis and 100 per cent efficacy against severe Covid-19 disease.
- Serum Institute of India Pvt. Ltd. (SIIPL) COVISHIELD™ Vaccine to prevent Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2. According to government data, the Covishield vaccine efficacy percentage of 70% has been seen in patients after its two doses. In one estimate, 100% efficacy has been observed after both doses of this vaccine. Covishield has been prepared using the viral vector platform where a chimpanzee adenovirus – ChAdOx1 – has been modified to enable it to carry the COVID-19 spike protein into the cells of humans. Well, this cold virus is basically incapable of infecting the receiver but can very well teach the immune system to prepare a mechanism against such viruses. The exact technology was used to prepare vaccines for viruses like Ebola and a number of studies have focused on viral vector vaccines against other infectious diseases such as Zika, flu, and HIV.

Legal Regulations of Vaccines

A vaccine comes under the definition of 'new drug' as defined under Section 2 cause (w) in New Drugs and Clinical Trials Rules, 2019 (CT Rules). The Central Drugs Standard Control Organisation (CDSCO) is the apex regulatory body in India. It is under Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India is the National Regulatory Authority (NRA) of India.

In accordance with the 2019-CTRules, the Drugs Controller General of India (DCGI), who heads the Central Drugs Standard Control Organization (CDSCO), is responsible for reviewing and approving clinical trial applications for all new drugs, investigational new drugs (INDs), and imported drugs to be registered in India. Additionally, per the 2019-CTRules, the G-ICMR, and IND-31, the DCGI and a DCGI-registered ethics committee (EC) must approve a clinical trial application prior to the sponsor initiating the trial, except in the case of non-regulatory academic/research clinical trials that only require EC approval. The DCGI review and approval process may be conducted in parallel with the institutional or independent EC review for each clinical trial site. CDSCO must confirm that the EC approvals for each participating site have been obtained per the protocol prior to approving the initiation of the study.

The Drugs and Cosmetics Act, 1940 and rules 1945 have entrusted various responsibilities to central & state regulators for regulation of drugs & cosmetics. Under the Act, CDSCO is responsible for approval of Drugs, Conduct of Clinical Trials, laying down the standards for Drugs, control over the quality of imported Drugs in the country and coordination of the activities of State Drug Control Organizations by providing expert advice

with a view of bring about the uniformity in the enforcement of the Drugs and Cosmetics Act. Therefore, all the regulations related to Drug Development and the stages of Pre-Clinical Trial, Clinical Trial and it's four phases, FDA Approval, Post Marketing and Drug Safety Monitoring shall be binding in case of vaccines also. Although, in times of pandemic the emergency guidelines have speeded the process and CDSCO circulars allowed rebates on import and exports of drug.

Conclusion

Vaccination technology is a boon which has emerged from the Biotechnology processes. Vaccination drive has proven to be a successful weapon in the past for the immunology against various fatal and virulent diseases like Measles, Meningococcal A, H1N1, Rotavirus, Hepatitis B, Rabies, Influenza, Polio etc. Today the world needs armour against the foe named Covid-19. To achieve this protection various pharmaceutical and Biotechnological Companies together with unsung Scientists worked day and night to make these vaccines available on such large scale for masses.

Pharmaceutical company like Pfizer, Pharmaceutical & Biotechnology Company like Moderna, Janssen Biotech Incorporation have become the face of covid vaccine drive across US. While in India, Serum Institute of India Biotech Co. being the World's Largest Vaccine Manufacturer producing Covishield Covid Vaccine and Bharat Biotech Co. which are not even meeting the domestic requirements but, have donated or sold 66 million doses a month ago across various countries like Bangladesh, Sri Lanka, Africa etc. In light of the data (Fact Sheet) adduced and WHO listings, talking biologically, we have come to the conclusion that the efficiency rate of mRNA Vaccine and Viral Vector Vaccine is much higher than the traditional Weakened Attenuated Vaccines. That's why, Pfizer, Moderna and Covishield are ahead in the race for human vaccines in the present day. In India we need more comprehensive outlook on regulations by CDSCO and FDA for speedy and safe drug discovery and development.

By the end of May 2021, 50% of the US population has received its first dose and 40% of the population i.e., 13 crores have been fully vaccinated. In India, 11% of the population has received its first dose and 3% of the population i.e., 4 crores have been fully vaccinated. Although we may find close figures in respect of the first dose of vaccination, 16 crores in US and 15 crores in India so far. Hopefully, through the good statistics of people who have recovered from the Covid 19 and the people who have received their doses of vaccination, we shall be able to achieve what's called as the "Population/Herd Immunity" by the Centre for Disease Control and Prevention (CDC).

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