



Vaccines and Therapeutics: Quality System Approach to Clinical Applications

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Abstract

Molecular bio-science developments involve applications of mRNA vaccines focused on diagnostic, prophylactic, and therapeutic aspects of COVID-19 related infectious diseases. These applications offer potential solutions for many of the current challenges in treating virus related infectious diseases. The goal of vaccine design and development is to manufacture and consistently produce a vaccine that is safe and effective. The vaccine discovery starts with design input in terms of identification of etiologic agent, immunogenicity, adjuvant, basic scientific concepts, non-clinical and clinical studies, and finally vaccine licensure (FDA approvals). The Lipid Nanoparticle Technology (LNT) for messenger RNA is being used for COVID-19 vaccines. This technology comprises of identifying and mapping signature features of the virus which encompasses the readability of the virus's blueprint, its neutralization and activation processes in order to deliver antibody proteins to protect the vaccine recipients' bodies from encounters with the virus. The administering regimens are studied in clinical research laboratory and study materials are tested in suitable bench testing and biological models projecting vaccine candidate's prophylactic immune response that is safe and effective. The vaccine manufacturing process requires critical quality control points (CQCPs) monitoring in order to maintain the stereochemical and immunological characteristics of the vaccine molecules and enable production of the vaccine in increasingly dosage quantities for ultimate human use. These aspects of vaccine development are well integrated into the total vaccinology life cycle (TVLC) regulatory requirements. The ultimate regulatory safety and efficacy requirements of the vaccine are proven through phases of clinical trials (class I, II, and III studies). The final process for human use to produce safe vaccine is part of pivotal clinical trials and data under the US FDA's premarket approval process for full-scale production and availability of safe vaccines for clinical use.

Keywords: mRNA Vaccines, Diagnosis, Prophylaxis, Therapy, COVID-19

Introduction:

The term "Vaccinology" encompasses the whole process of producing vaccines inclusive of basic scientific concepts, preclinical, clinicals and approvals for human intended use. The design of clinical trials is based on US FDA's regulations. Vaccines are defined as immunogenic preparations that create an immune response to the disease in humans. The basic concept of vaccines emerged from the preparations that contained the microbes that contained the same structural characteristics of microbes that cause disease. Modern vaccines incorporate recent developments in immunogenomics, bioinformatics, and molecular aspects of the therapeutic preparations. These preparations are administered to human beings to produce or increase immunity to a particular disease organism. The usage of these preparations has extended the applications to include the intended use for active immunologic prophylaxis (e.g., preparations of killed microbes of virulent strains or living microbes of attenuated strains or their derivatives or products). Methods of vaccine administration vary and accordingly inoculation being the most common. An administered vaccine stimulates the immune system to produce antibodies exactly like it would as the injected person was exposed to the disease. After getting vaccinated, an injected person develops immunity to that disease without having to get the onset of that disease. This is why vaccine

preparations are considered as powerful medicine tools as preventive measures.

This review article focuses on developmental aspects of pandemic situations. Multiple disease outbreak models have been identified to evaluate impact of virus particles and various therapeutics on safety and effectiveness. Estimating the scope of a disease outbreak must address consideration of factors such as population susceptibility, effective/ineffective dose, incubation period, modes of transmission, duration of illness, mortality rate, effectiveness of treatment interventions and population migration. Environmental systems comprise of the release of epidemiologic agents before the onset of symptoms in exposed subjects. Such systems have been reported for the detection of the type of viral mutants in the atmosphere in indoor and outdoor settings. Testing technological products are being developed and used for these types of infectious disease agents detection based on real-time polymerase chain reaction (PCR) methodology. Available testing technologies are based on detecting an environmental biological agent (i.e., virus particles). An ideal testing situation is dependent on accuracy, sensitivity, and specificity of the testing methodology dependent on efficiency of the sample collection system comprising of location and placement of the monitors, and the concentration of the organism in the air sampled by the collector. Rapid and accurate diagnosis of potential viral agents is crucial for identifying and lessening

the impact of infectious threats. A major effort is to enhance diagnostic capacity in the Laboratory Response Network (LRN), established by the Center for Disease Control (CDC).

This article focuses on new developments and issues related to the use of vaccines. Monitoring systems using PCR and antibody-conjugated-technology have greater sensitivity and specificity for biological agents' detection. This includes the latest information on vaccines, including updated recommendations for vaccination across the lifespan and innovative and practical strategies for ensuring timely and appropriate vaccination. From scientific discovery, development to safety monitoring, few preventive measures are considered. Current vaccines are designed as therapeutics as COVID-19 diseases are spread from person-to-person, and vaccines can induce not only protection for individuals but community as well (i.e., herd, or community immunity). This includes designing and testing those individuals that are part of clinical trials and meeting NIH, CDC, and FDA's approvals.^{1,2}

Discussions:

Stem Cell and Gene Therapies continue to be at the very center of healthcare innovations and are the fastest-growing fields of vaccine development and clinical applications. Continuous clinical trials are transforming how to treat COVID -19 Omicron subvariants (i.e., BA.1, BA212.1, BA.4, BA.5) and how certain variants are treated and potentially cured significantly changing healthcare outcomes in certain populations. The U.S. FDA has approved certain vaccines for emergency use (<https://www.grandviewresearch.com/industry-analysis/cell-therapy-market>). Literature for regulatory applications points to a rapid availability in cell and gene therapy developments. The vaccine developers are transitioning from early manufacturing to immediate availability of specific vaccines for Omicron subvariants as they are detected in certain patient populations¹⁻⁶. This will create tremendous burden on healthcare economics in the near future in terms of manufacturing cost, challenges for pharma and biotech industries. These economic factors will be focused on several aspects, such as increasing demands on the availability of manufacturing of batch sizes, standardizing and streamlining global processes, and reducing the cost of vaccine materials used in manufacturing processes. This will be embedded in developing processes that provide high quality yields of consistent vaccine products.^{1,2,4,6}

The efficacy of a gene therapy is based on the delivery mode and its ability to deliver a gene into target cell populations. A variety of therapy products have been developed attempting to improve the effectiveness of the vaccines and pharmaceuticals (Paxlovid). However, most clinical trials to date have employed viral vectors for the delivery of genetic materials as they are capable of efficiently transducing cells and are claimed to achieve reasonably long-term expression of the desired genes to deliver sustained therapeutic effects. There are projections to be made around the optimal vector effectiveness from holistic viewpoint of the therapies'capabilities, scalability and end-use.^{3,4,5,7} Most people have been exposed to adenovirus at some point in their lifetime (i.e., common cold), and the immune system recognizes it and puts up a defense before transfection can take place in most cases. It is pointed out that there has been research done using Adenoviruses as the viral vector platform for vaccines (i.e., J&J COVID vaccine).

Vaccine Design Controls:

Adjuvants to a particular vaccine product formulation that affects the action of the active ingredients have been used to improve the immune responses to vaccines. In this process, the role of adjuvants plays a key role for the safety and

effectiveness of the vaccine for human use. In order to be efficacious, a vaccine must stimulate the development of both inborn and acquired immunity. To stimulate inborn immunity for designing vaccines in a human cell is an important feature for the effective immune responses following vaccination. Most of today's vaccines contain adjuvant ingredients that enhance the effectiveness of treatments. Inborn immunity and acquired immunity are linked through antigen-sensitizing cells (ASCs), in particular macrophages and dendritic cells. In inborn immunity developments, these cells specialize in uptake of antigens and contain a variety of pattern recognition receptors, which facilitate the recognition of pathogenic molecular patterns (i.e., viral nucleic acids patterns). As macrophages and dendritic cells begin to mature in the draining lymph nodes they adhere to lymphocytes as part of the specific or acquired immune response. Thus antigen presentation is mediated by a sequence of signals emitted by antigen followed by other signals provided by co-stimulatory molecules and secreted cytokines, which contribute to the development of acquired immune response. Thus it is the nature of the antigen (i.e., virus particles) signals at the initial site of infection that generates the immune system with the necessary information regarding the viral antigen providing the type of immune response needed to control the infection. The activation and maturation of dendritic cells involve independent or synergistic actions to secrete cytokines as well as pattern recognition receptors response. Integration of the host response to pathogenic-associated molecular patterns provides a specialized tailored response; therefore, it is recommended to design vaccines to stimulate complementary signaling pathways to mimic the virus structure as it occurs in the natural environments. Vaccine components should align to dendritic cells response at the site of vaccination so that the type of immune response can be achieved to establish effective immunity and immunologic response to infection. The scope of modern vaccines has widened considerably based on genomic vaccine developments.

Synthetic Nucleic Acid Vaccine preparations contain not only the m-RNA segment of the vaccine but other components (vaccine excipients) are designed to maintain the vaccine potency. The stability of the vaccine over time and specified temperatures is an important consideration. The hard core of m-RNA vaccine structure must retain stereochemical capability of equivalency to retain human system related viability from the time it is prepared to the time it is administered to the individual person, and it must retain equivalent viability when stored and transported for the specified periods of time. For synthetic (non-living) vaccine preparations, immunogens must retain the original conformation that induces a protective immune response. The design of vaccine studies has moved from childhood infections to infectious adults and senior citizens. It is critical that new vaccines are developed to prevent infectious disease variants caused by infectious agents that antigenically change for newly emerging variants.^{3,4 6}

Vaccines provide an effective means to prevent and control transmission of serious infections in the human population for the safety of public health. The vaccine development techniques in genetic engineering and m-RNA have made it possible to produce safer and more effective vaccines; however, mixing vaccines must be done with care so that the immunogenicity and safety of each component is not compromised. The process by which m-RNA vaccines are designed are based on vaccine epitopes via computational analysis of the genome sequence of the virus. The mechanism of the vaccine that is administered containing mRNA molecules that contain the gene encoding the antigen under the control of appropriate promoter and specific sequences allows the transcription and translation by the host cell needs to be part of design control studies protocols. The RNA

molecule can be engineered to encode protein adjuvants such as cytokines in the clinical studies for human use. The relative balance of cell-mediated immunity versus humoral mechanisms, such as synthesis of antibodies, can be important for protection of vaccinees. The rate the infectious diseases are transmitted between individuals in the community is affected when a significant proportion of the population is vaccinated.^{3,4 6}

Developments of vaccines provide an effective pathway to prevent and control transmission of COVID-19 related infections in humans. In addition to protection and immunization of the individual, the rate that COVID-variants are transmitted between individuals in the community is dependent on when significant proportion of the population is vaccinated. It is important that new vaccines are developed to control infections caused by new genetic variants that antigenically change (i.e., delta and omicron variants). It has been reported in the literature SARS (severe acute respiratory syndrome) and its intermittent viral pieces and units (i.e., virus reassortments) make jumps from adults to pediatric populations. The CRISPR/Cas9 gene editing technology offers challenging opportunities to design specific vaccines for omicron variants. This technology consists of CRISPR guide RNA bound by the Cas protein to the targeted sequence of omicron subset.⁵

Vaccine Regulatory Pathway:

This section describes key components in the design and development of COVID-19 vaccines with regard to insights into strategies to create and produce vaccines addressing vaccine antigenic structures' immunogenicity in terms of sensitivity, specificity, safety and efficacy. The manufacturing process requires basic scientific antigenic design controls, purity of the materials, safety and efficacy information. Once the nonclinical structural studies are completed, an investigational new drug (IND) application containing laboratory study results of the vaccine candidate is compiled and submitted to the US FDA (Food and Drug Administration) to request permission to conduct clinical studies in humans.¹⁻³

General Considerations and Strategies for Vaccine Development:

Vaccine development involves procedures and processes that include nonclinical and clinical studies, licensing, and approval.^{1,2} In these developmental processes, vaccine potency is established as the ability of the vaccine product to perform as claimed and to associate with the measurable output effect and/or correlate with qualitative/quantitative aspects of in-vitro testing. The concepts of vaccine preparation and purity is part of the regulatory design controls requirements free from such materials as pyrogens, adventitious agents, and chemical contaminants in the manufacturing process of the vaccine end product. Safety of the vaccine product is important to provide freedom from side effects that could be harmful to vaccinees in relation to the abnormal conditions of the recipient. Thus vaccine safety is relative in individual populations in a defined community. On the other hand vaccine efficacy is related to reduction in disease incidence closely related to a specific person / subpopulation. Development of new vaccines such as COVID-19 vaccines started with the concept that immunization can prevent or modify a clinical infectious disease of unknown epidemic origin. The challenges involved are complex and require specialized GMPs (Good Manufacturing Products) facilities approved by global regulatory agencies. This challenge becomes important for a vaccine such as COVID-19 vaccines with wide utility, with manufacturing of tens of millions of doses required. The goal is that each and every dose is equivalent, safe, and effective. The regulatory burden is

the level of proof and documentation essential to provide guaranteed overall effectiveness achievable for every vaccine's lot and effective doses. The Investigational New Drug (IND) application allows a pharmaceutical manufacturer to conduct clinical studies. The IND application allows the vaccine manufacturer to initiate and conduct the safety of the clinical trial subject as a primary concern of the CDC and FDA regardless of the phase of clinical study. These agencies evaluate the protocols in order to ensure overall safety and effectiveness of the vaccine's clinical utility.^{1,2}

The design controls require understanding of the concept of COVID-19 viral antigenic structure of the infectious agent and epitopes on structural proteins. This step is required prior to vaccine's overall clinical investigation plan (this involves identification of vaccine antigens, overall clinical investigation plan through vaccine manufacturing process controls). How the vaccine is produced requires essential genetic engineering process and combination of methods. During and after the manufacturing process, testing must be done to document that a vaccine lot is pure, potent, stable, safe and efficacious. The central point related to genetic engineering is the evolution of a procedure used to make RNA based vaccine from the laboratory into a process that can be scaled up to operate in a manufacturing control to make tens of millions of doses of the vaccine. However, this part of making vaccine is the beginning of the FDA's new drug application (The NDA is a regulatory requirement designed to provide the FDA with adequate information to consider pre-evaluation of the data for the NDA document). Genetically unstable viral particles have highly mutable and unstable immunological epitopes that interact immunological reactions to viral particles and determine half-life viral protective immune response by RNA derived vaccines. During the vaccine development, the initial clinical studies (phase I) focuses on safety aspects of vaccine dose required to stimulate immune response and phase II focusing on immunization schedule. Phase III studies are pivotal for safety and efficacy dose schedule for immunization in a defined population in order to document that the vaccination data shows to prevent the disease.

Manufacturers of biologics must hold a license for products, which are reviewed by the FDA's Center for Biologics-CBER (Biologics License Application -BLA). A BLA protocol is used through the official BLA form designated as 365h and has similarity to the NDA form. Data on products characterized as biologics are reviewed by the FDA's CBER staff; however, the FDA's Center for Drug Evaluation (CDER) has a role to play for certain therapeutic biologic products that were transferred from the CBER. The CBER has large regulatory responsibilities in vaccine developments in addition to tissue safety, and blood products. Vaccines are considered by the US FDA in the category of biologics and are regulated under the following regulatory statement:

Federal Regulations 21 CFR 600.3

Biological product means any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, applicable to the prevention, treatment, or cure of disease of conditions of human beings.

As discussed in this article, the critical responsibilities of regulatory pathways of an IND and BLA approvals are important and critical steps in development and evaluation of vaccine products for diagnosis, prevention, or treatment of COVID-19 infections. The responsibilities and processes of regulatory approval are designated at the hierarchy of FDA's management in a manner based on understanding and compliance expertise in vaccinology. A clinical protocol content and format is described in 21 CFR Section 312.23. It describes how a particular clinical trial is to be conducted. It

describes the objectives of the study, the trial design, the selection of subjects, and the manner in which the trial is carried out. Previous human studies and clinical data analysis with the vaccines is essential for the review and evaluation of the new vaccine products 21 CFR Section 312.23 (a) (9). Summary information should describe the study design and indicate the following for each group: the vaccine dose, route and schedule of administration; age, sex, general health, and the number of subjects studied; enumeration of the clinical and laboratory parameters that were monitored; and the relevant presentation of results.

Clinical Evaluation of Vaccines:

Phase I studies are conducted for human use. The primary goal of phase I studies is to identify structural design of the COVID-19 virus. This phase follows identifying epitope markers for the immune response. Phase I studies are often performed in situations where the subjects can be closely monitored. Phase II studies only begin after the data demonstrating tolerability and safety is demonstrated from the phase I studies. These studies are designed to assess vaccine immunogenicity (efficacy), as well as the projected safety assessments on a large group of subjects. The criteria for subjects may be the actual group categories for the vaccine such as children or elderly. Phase II studies are designed to assess level of immunogenicity and/or efficacy while the main objective of these studies include determining the optimum effective dose. Data from these studies also reflects the benefit-to-risk ratio, which feeds into the design of the phase III studies. Phase III studies are designed as randomized multicenter trials incorporating larger groups of vaccinees (approximately 300-3000 participating subjects). These are pivotal studies designed to document immunogenicity or efficacy. Phase IV studies include assessing data on side effects, duration of protection, herd immunity. Phase IV post approval (US FDA) surveillance studies include effects of COVID-19 vaccine on certain target population (i.e., pregnant females, rare diseases or specific adverse events).^{3,4}

Conclusion:

Clinical trials are an important part of vaccine development. There are four phases of clinical trials. The first three are required to document safety and efficacy (phases I, II, and III). The fourth phase is conducted after licensure and marketing to monitor essential information about total effectiveness of COVID-19 vaccine and its expected indication for use results. Vaccines are regulated by the FDA's Center for Biologics Evaluation and Research (CBER). The data from clinical trials ensures the rights and safety of vaccinees and demonstrate favorable risk-benefit profile for the US FDA to license the vaccine.

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Biography:

Dr. Kaiser J. Aziz-Andersen completed a 30-year career with the FDA as a clinical regulatory scientist and manager of drug and device evaluations, approvals, good manufacturing and quality system applications. Prior to joining the FDA, he developed and implemented quality assurance standard operating procedures and protocols for medical diagnostic systems in hospitals, physicians' offices, and clinical reference laboratories. During his tenure at FDA, served as adjunct faculty in the department of Medicine and Physiology, NIH Graduate School, where he developed and taught courses in Clinical Pharmacology, Therapeutic Drug Monitoring, and Clinical Laboratory Medicine. Currently, he serves as an adjunct faculty at Virginia Polytechnic Institute and State University's Medical HACCP Alliance Program, where he teaches Quality Risk Management courses and workshops based on Global HACCP standards for the Pharmaceutical industry. He was an invited guest editor on Nanotechnology and Clinical Trials in the journal of Clinical Ligands Assay. He is the author of book chapters, textbooks, and over 70 publications in professional and trade journals. His expertise includes Quality System Approach to Medical Device and Pharmaceutical Premarket Applications.