VOLUME - 12, ISSUE - 04, APRIL - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper | Clinical Research

REGULATION AND TESTING OF VACCINES

P. Gomathi — B. Pharmacy
K. Akalya — 4th Year

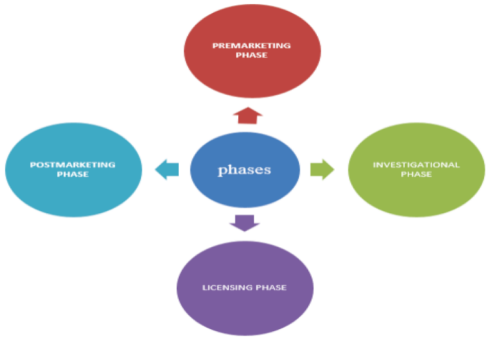
ABSTRACT Vaccines are one of the most significant achievements of science and public health. Vaccines for prevention of infectious diseases are regulated by the U.S. Food and Drug Administration (FDA) and the legal framework for regulation is derived from Section 351 of the Public Health Service Act and from certain sections of the federal Food Drug, and Cosmetic Act (FD&C Act). Vaccines are a unique class of pharmaceutical products that meet the statutory definition of both a drug and biological product. Vaccines are a unique class of pharmaceutical products that meet the statutory definition of both a drug and biological product. The primary responsibility of NRAs is to ensure the quality, safety, and effectiveness of pharmaceutical products. The implementation of a strong regulatory system will facilitate these goals, which are especially critical for vaccines that are inherently more difficult to develop, characterize, and manufacture than most pharmaceutical products. The Federal Drug Administration (FDA) has developed a managed review process that provides regulatory oversight through all phases of vaccine development. Advances across a wide range of scientific disciplines have enhanced the prospects of developing new and better vaccines. Novel vaccine approaches such as recombinant vaccines and novel adjuvant and delivery systems pose regulatory challenges for NRAs. However, The NRAs should be dynamic and flexible entities, as they strive to develop regulatory requirements to address the evolving science. Further, NRAs must be prepared to address public health emergencies that will require expedited approval mechanisms, such as biological terrorist events, pandemic influenza, and other EIDs.

KEYWORDS : Vaccines, Pharmaceutical products, Recombinant vaccines, Dynamic, NRA.

INTRODUCTION

Vaccines are one of the most significant achievements of science and public health. As a result of successful vaccination programs and campaigns, many vaccine-preventable diseases are now uncommon in the United States. Vaccines for prevention of infectious diseases are regulated by the U.S. Food and Drug Administration (FDA) and the legal framework for regulation is derived from Section 351 of the Public Health Service Act and from certain sections of the federal Food, Drug, and Cosmetic Act (FD&C Act).[1] The FD&C Act defines drugs, in part, by their intended use as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease."[2] Thus, vaccines are a unique class of pharmaceutical products that meet the statutory definition of both a drug and biological product. Prophylactic vaccines differ from many other drugs and biological primarily in how they are administered to a large population, in particular, young healthy people to prevent rather than treat disease, their mechanism of action, and their risk/benefit profile. Although subject to the same regulations as other biological products, vaccines are inherently more difficult to develop, characterize, and manufacture than most pharmaceutical products.

Stages Of The Regulatory Review Of Vaccines Products



Premarketing Phase

The regulatory requirements for biological products cover the entire life-cycle of the product from the pre-IND stage, through the premarketing (consisting of the various IND phases and pre licensure) and post marketing stages. The pre-IND stage consists of laboratory development, preclinical testing of candidate vaccines, and development of the manufacturing process.

The clinical development of a new drug in the United States usually begins with a sponsor approaching the FDA for permission to conduct a clinical study with an investigational product through submission of an IND application form. These requirements can be found in the IND regulations.[3]

Investigational Phase

Only licensed vaccines may be shipped from one state to another; however, during the premarketing phase, interstate shipment of products for investigational use is allowed under the law and regulations. There are generally three separate phases in the clinical evaluation of experimental biological at the premarketing stage. These phases may overlap, and the clinical testing may be highly iterative because multiple Phase I or Phase II trials may be performed as new data are obtained.[4]

Licensing Phase

Following completion of IND studies demonstrating the safety and efficacy of the vaccine for a specific use and population the sponsor can submit a BLA to obtain a license for a new vaccine under section 351 of the PHS Act for commercial manufacture and distribution of the product. Prior to the submission of a BLA, a pre-BLA meeting with the FDA is strongly encouraged to discuss the sponsor's product development plan. For the FDA to provide sponsors with advice regarding the adequacy of information to support a BLA

Postmarketing Phase

If the manufacturer wishes to significantly modify the approved manufacturing process or directions for vaccine use, prior approval must be obtained from the FDA before these changes can be implemented. The applicant is required to submit an account of these changes to the appropriate license applications.[5]

Vaccine Testing

Vaccines are tested during the pre licensure as well as the post licensure phase. Testing procedures are developed from a combination of the understanding of past adverse experiences and the best current knowledge regarding the potential for new ones. From past experience, a few highly important issues must continue to receive special attention [6] All vaccines require an extensive search for extraneous contaminants. The experience in which human serum was used as a stabilizer for yellow fever vaccine and caused hundreds of cases of long-incubation hepatitis virus infection underscored this need[7] The FDA requires that cell substrates and vaccine viral seeds used in production be appropriately selected and tested to ensure that they do not introduce any unintended risks. The current cell substrates used to manufacture licensed vaccines are primary avian or monkey cells, diploid cells, one continuous cell line, Vero, as well as yeast and insect cells [8]

If a vaccine is manufactured in a cell substrate that is derived from a tumor, or that has developed a tumorigenic phenotype through an unknown mechanism, it could carry a higher theoretical risk of containing oncogenic substances.The epidemic of bovine spongiform encephalopathy (BSE, also referred to as mad cow disease) and its possible relationship to human variant Creutzfeldt-Jakob disease (VCJD) has been of special concern. [9] The recombinant DNA era, the possible risk of induction of transformation of cells of the recipient was a major concern. This issue has been approached by careful study of the constructs used and the stability of these constructs and by attempts to reduce extraneous DNA content to levels that are regarded as extremely unlikely to produce an adverse genetic event.[10][11][12]

Adverse Event Monitoring

An adverse reaction to a biological product is defined as an event associated with the use of a biological product, regardless of whether it is considered product related, and it includes any side effect, injury, toxicity, or sensitivity reaction or significant failure of pharmacologic action. Adverse reaction reports come from several sources. The results of reported adverse reactions associated with vaccine use are compiled and entered into the Vaccine Adverse Event Reporting System.[13] The NCVIA also mandated the development of vaccine information sheets for distribution by health care providers to each adult or to the legal representative of each child receiving any vaccine recommended for routine pediatric use by the ACIP. This effort was made to ensure that sufficient written information about the risks from the diseases and the risks and benefits of vaccines would be provided.[14]

ProductionLabellingAndAdvertising

Labeling changes are usually initiated by the manufacturer but may be initiated by CBER. Historically, manufacturers have had to obtain prior approval from CBER before the labeling changes were made.[15]

SpecialConsiderations

Combination Vaccines:

Combination vaccines are composed of two or more antigens that are intended to induce protection against multiple infectious diseases or several different serotypes of the same organism.(16)

Vaccines To Counter Emerging Infectious Diseases And Biothreat Agents:

Immunization programs in the United States have been remarkably effective at reducing morbidity and mortality from the most common naturally transmitted infectious diseases (e.g., polio, measles, and diphtheria). However, emerging infectious diseases (EIDs), from pandemic influenza to severe acute respiratory syndrome, and biological threats that have the potential to be intentionally released into the general population also pose a threat to global public health.[17]

Emerging Post – Licensure Issues

Detection Of Porcine Circoviruses In Rotavirus Vaccines

Inadvertent contamination of vaccines with extraneous infectious agents is a major safety challenge and inherent risk in the manufacturing process.[18] The FDA Final Guidance for Industry entitled, *"Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications".*[19] The final step in IPV production involved formalin inactivation of poliovirus. SV40 is relatively resistant to formalin inactivation and thus low levels of live SV40 remained present in lots of IPV.[20]

CONCLUSION

The primary responsibility of NRAs is to ensure the quality, safety, and effectiveness of pharmaceutical products. The implementation of a strong regulatory system will facilitate these goals, which are especially critical for vaccines that are inherently more difficult to develop, characterize, and manufacture than most pharmaceutical products. The FDA has developed a managed review process that provides regulatory oversight through all phases of vaccine development. Advances across a wide range of scientific disciplines have enhanced the prospects of developing new and better vaccines.

Novel vaccine approaches such as recombinant vaccines and novel adjuvant and delivery systems pose regulatory challenges for NRAs. However, NRAs should be dynamic and flexible entities, as they strive to develop regulatory requirements to address the evolving science. Further, NRAs must be prepared to address public health emergencies that will require expedited approval mechanisms, such as biological terrorist events, pandemic influenza, and other EIDs.

Abbrevation

ACIP	Advisory committee on immunization practices
BLA	Biologics license application
BSE	Bovine spongiform encephalopathy
CBER	Center for biologics evaluation and research
DNA	Deoxyribonucleic acid
EID	Emerging infectious disease
FDA	Federal drug administration
IND	Investigational new drug
IPV	Inactivated poliovirus vaccine
NCVIA	National vaccine childhood injury act
NRD	Nation recruitment agency
PHS	Public health service
U.S	United state
VCJD	Variant Creutzfeldt-Jakob disease

REFERENCES

1. Food Drug and Cosmetic Act. 21 USC §321.
2. Public Health Service Act. ch 373, title III, §351, 58, Stat. 702, 42 USC §262 (1944)
3. Code of Federal Regulations. Title 21, Part 312. Washington, DC, Office of the Federal Register, National Archives & Records Administration; 2015.
4. Vaccines and Related Biological Product Committee (VRBPAC) Meeting Transcript, May 26-27. 1998.
5. U.S. Food and Drug Administration Post marketing studies for approved human drugs and licensed biological products; status reports. Fed Regist. 2000;65:64607–64616.
6. Fox J.P., Lennette E.H., Manso C. Encephalitis in man following vaccination with 17D yellow fever virus. Am J Hyg. 1942;36:117–142.
7. Fox J.P., Manso C., Penna H.A. Observations on the occurrence of icterus in Brazil following vaccination against yellow fever. Am J Hyg. 1942; 36:68–116.
8. . Marwick C. BSE sets agenda for imported gelatin. JAMA. 1997; 227:1659–1660.
9. Marwick C. BSE sets agenda for imported gelatin. JAMA. 1997; 227:1659–1660
10. Center for Biologics Evaluation, Research, Congressional, Consumer, and International Affairs Staff. US Food and Drug Administration; Rockville, MD: 1985. Points to consider: production and testing of new drugs and biological produced by recombinant DNA technology. HFB-142.
11. Center for Biologics Evaluation, Research, Congressional, Consumer, and International Affairs Staff. US Food and Drug Administration; Rockville, MD: 1985. Points to consider: production and testing of new drugs and biological produced by recombinant DNA technology. HFB-142.
12. Center for Biologics Evaluation and Research, Congressional, Consumer, and International Affairs Staff. US Food and Drug Administration; Rockville, MD: 1992. Points to consider in the production and testing of new drugs and biological produced by recombinant DNA technology: nucleic acid characterization and genetic stability.
13. Vaccine Information. 42 United States Code, Sec. 300Aa-26.
14. New vaccine information materials. Fed Reg. 1994; 59:31888.
15. Pittman M. Instability of pertussis-vaccine component in quadruple antigen vaccine. JAMA. 1962; 181:25–30.
16. Falk L.A., Midthun K., McVittie L.D. The testing and licensure of combination vaccines for the prevention of infectious diseases. In: Ellis R., editor. Combination vaccines. Humana Press; Totowa, NJ: 1999. pp. 233–248.
17. US Department of Health and Human Services. 2010. The public health emergency medical countermeasures enterprise review transforming the enterprise to meet long-range national needs. August.
18. *Code of Federal Regulations.* Office of the Federal Register, National Archives & Records Administration; Washington, DC: 2012. Title 21, Part 610.13.
19. Center for Biologics Evaluation and Research, Guidance for industry. US Food and Drug Administration; Rockville, MD: 2010. Characterization and qualification of cell substrates and other biological materials used in the production of viral vaccines for infectious disease indications.
20. Gerber P., Hottle G.A., Grubbs R.E. Inactivation of vacuolating virus (SV-40) by formaldehyde. Proc Soc Exp Biol *Med.* 1961; 108:205–209.