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Veterinary Vaccines- Harmonization of Veterinary Vaccines Monographs of Indian Pharmacopoeia (IP)

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ABSTRACT

India is a country with a large livestock and poultry resource. These resources play an important role in improving the socioeconomic conditions of rural farmers. Monitoring livestock health, as well as disease detection and control with effective vaccines, is the most effective strategy to maximize livestock production and minimise losses due to disease morbidity and mortality. Vaccines form the divergent group of biopharmaceutical products which are manufactured according to the pharmacopoeial standards. Pharmacopoeial standards are the minimum of requirements that a company must meet before releasing a product for sale or distribution. Pharmacopoeial standards must be harmonised, as they are a crucial instrument for marketing permission, market surveillance, and the free flow of drugs between regions and nations. Therefore, the necessity of developing global quality standards for drugs, which ultimately aim at pharmacopoeial harmonization, is expanding as a result of globalization and the expansion of international trade.

Keywords: Pharmacopoeia; Harmonization; Veterinary; Vaccines; Restructuring; Monographs

Introduction

Vaccines are a diverse group of pharmaceuticals that contain immunogenic ingredients that can trigger a specific, protective immune response to infectious diseases. These could be created using toxins from bacteria, viruses, parasites, or other appropriate species. As antigens, vaccines may include live, attenuated, avirulent, inactivated, or dead microorganisms. Some vaccinations are made up of antigenic fractions or chemicals that are made by the same pathogenic bacteria, but are rendered harmless while still being immunogenic. The microorganisms used to make vaccines can come from a single species, two species, or more. Recombinant DNA technology could be used to produce the antigen. Vaccines may be produced following the procedure detailed in the designated monograph or by using an alternative approach, assuring that the integrity of the antigen is maintained and that the products are devoid of any microbial impurities or extraneous materials. When vaccinations are made, appropriate adjuvants can be added. Antibiotics are often only added to materials used in cell culture media, material taken from skin or other tissues, and egg innocula during the production process. Vaccines may, if necessary, be preserved or treated with an appropriate bactericide. The finished goods are distributed under aseptic conditions and then sealed to prevent the entry of any foreign bacteria. However, as mentioned in the monograph, the final vaccine can be dispensed in single-dose or multiple-dose vials [1].

Veterinary biological products include vaccines, serums, immunosera, and other similar products that are formulated to induce active or passive immunity, assess the level of immunity, or detect diseases or health issues in animals. The procedure of immunizing a household, livestock, or wild animal is known as animal vaccination. The practice is related to veterinary medicine [2]. Louis Pasteur developed the initial vaccine for chicken cholera in 1879, marking a significant milestone in the history of animal vaccines [3]. Vaccines are classified into traditional and advanced generation vaccines [4]. Implementing animal vaccination has produced remarkable results, establishing it as the primary and lasting strategy for combating infectious veterinary diseases [5]. India has a significant resource of

livestock and poultry, which plays a crucial role in improving the socioeconomic status of rural farmers. Monitoring health, diagnosing diseases and controlling them through effective vaccines are the key to increasing livestock productivity and reducing losses from disease morbidity and mortality. Ongoing research and development in veterinary biologicals have led to the successful eradication of major diseases such as rinderpest, African horse sickness, and contagious bovine pleuropneumonia in the country [6]. Various bacterial and viral diseases that affect cattle, buffaloes, sheep, goats, pigs, and poultry are being controlled through prophylactic vaccines created by the Animal Science Institutes of ICAR. These biologicals have been distributed to commercial manufacturers and state biological production units to ensure sufficient availability nationwide [7].

Indian Pharmacopoeia

Pharmacopoeia, a term derived from the Greek words "Pharmakon" (meaning drug) and "Poiea" (meaning to make), refers to an authorized and official publication issued by the government-appointed authorities in each country. As stated by the World Health Organization, there are currently 68 different Pharmacopoeias being effectively used in 66 countries worldwide [8]. It is an official book documenting medications or other pharmacological substances, including their usage, production, and control. It is legally binding scientific reference work that details the criteria and requirements for medications used in a particular nation or region and were created by a regional or national authority [9]. They are official publications that include international and national regulations and procedures that must be adhered to scientific and legal techniques, including the qualitative and quantitative measurement of active ingredients and excipients used in the manufacture of pharmaceuticals. The Pharmacopoeia is instrumental in safeguarding public health and ensuring the quality of drugs. It achieves this by combining recommended analytic procedures and specifications for excipients, pharmaceuticals, and dosage forms in its general sections and special monographs.

By translating scientific findings into common practice through the use of pharmacopoeial regulations, pharmaceutical analysis offers cutting-edge research which can directly impact the efficacy, quality, and safety of medicines [10]. Monographs in the pharmacopoeia detail the definition, description, appearance, production, identification, recognition-diagnostic analysis, physicochemical properties (such as solubility, boiling point, and melting point), quantification, biological properties (including biological activity and definition), packaging, and storage conditions of chemical, biological and biotechnological active and auxiliary substances, herbal/animal drugs and preparations, finished and medicinal products.

The Drugs and Cosmetics Act

The Indian parliament laid down Drugs and Cosmetics Act, 1940 which regulates the import, manufacture, and distribution of drugs in India [11]. The main goal of the act is to ensure the safety, efficacy, and compliance with the state quality standards of the drugs and cosmetics sold in India. In 1940, the legislation was approved and initially referred to as the Drug Act. The original act was prepared in accordance with the suggestions made by the 1930-formed Chopra Committee. The related Drugs Rules were passed in 1945. Since 1940, the act has undergone several amendments and is now known as the 1940 Drugs and Cosmetics Act [12].

The act is now referred to as the Drugs and Cosmetics some other goals:

- Licensing-based regulation of import, sale and distribution of drugs and cosmetics.
- Incorporation of exclusively qualified individuals in the distribution, import, and sale of medications and skincare items.
- Maintain high standards for medical care by preventing the appearance of substandard drug quality.
- Manufacturing and distribution of Unani, Siddha and Ayurvedic remedies.
- Establishment of the Drug Technical Advisory Board (DTAB) and Drug Consultative Committees (DCC) for allopathic and allied drugs, along with cosmetics [13].

The Drugs and Cosmetics Rules 1945

The Drug and Cosmetics Act of 1940 gave rise to the Drugs and Cosmetics Rules of 1945, which were subsequently adopted by the Indian government. These regulations provide instructions for the sale, exhibition, storage, and prescription of each schedule of pharmaceuticals, which are categorised according to specific schedules [12,14]. License requirements are described in detail in Rule 67. The labelling requirements can be found in Rule 97 [15]. The rules have also undergone periodic revisions in order to address changing needs and address any flaws that were found when they were being put into practise.

History of Indian Pharmacopoeia

The Indian Pharmacopoeia Commission (IPC) is entrusted with the task of releasing the Indian Pharmacopoeia (IP) in adherence to the provisions outlined in the Drugs and Cosmetics Act, 1940 and Rules 1945. This responsibility is carried out on behalf of the Ministry of Health & Family Welfare, Government of India. IP is acknowledged as the official standard-setting document for drugs produced and/or commercialized in India. IP includes several authoritative methods for analyzing pharmaceuticals and defining their identity, purity, and potency. The regulatory agencies implement the authorized IP standards to guarantee the high quality of drugs in India. The IP requirements are deemed legally acceptable during the process of quality assurance and in the event of a legal dispute. The history of the Indian Pharmacopoeia (IP) begins in 1833, when a commission suggested that a pharmacopoeia be published. The majority of the remedies

included in this pharmacopoeia, which was first published in 1844, are commonly used indigenous remedies. The pharmaceuticals from the British Pharmacopoeia and the indigenous remedies used in India were both covered in a later version published in 1868. In 1885, India officially ratified the BP. The publication of a National Pharmacopoeia was recommended in 1927 by a drug inquiry committee appointed by the government. The Indian Pharmacopoeia Committee was formed in 1948, after independence, with the publication of IP serving as its primary duty [16]. https://ipc.gov.in).

The Government of India established the IP Committee on November 23, 1948. The Central Indian Pharmacopoeia Laboratory (CIPL) was founded in 1965 as a subordinate office/laboratory of CDSCO under the Directorate General of Health Services (DGHS), Ministry of Health & Welfare. Drugs Controller was appointed as Member Secretary and Director CIPL was member of IP Committee. To help the IP committee, several other subcommittees were created. Along with other regulatory initiatives including Zonal testing of drug samples from India's northern zone, CIPL actively participated in the publication of IP-1985, IP-1996, and its Addendum in 2000 and 2002. The Ministry of Health and Family Welfare, Govt. of India, submerged the existing Central Indian Pharmacopoeia Laboratory along with the Indian Pharmacopoeia Commission. IPC is an autonomous fully funded agency located in the Ghaziabad NCR region as of January 1, 2009. The publication of the Indian Pharmacopoeia serves the purpose of advancing the goals set by the Indian Pharmacopoeia Commission. The objectives revolve around the formulation of all-encompassing drug monographs that will be highlighted in the Indian Pharmacopoeia. This encompasses dosage forms, active pharmaceutical ingredients, medical devices, pharmaceutical aids, and the regular revision of these monographs. The goal of the IPC is to advance public health in India by developing authoritative and formally recognized standards for the quality of drugs used by patients, consumers, and healthcare professionals, including dosage forms, active pharmaceutical ingredients and excipients.

The Vision of the Commission is

Guaranteeing the highest standard of pharmaceuticals for both humans and animals, while considering the practical constraints of current manufacturing and analytical technologies [17].

Mission

To improve public health and animal health in India through the establishment of recognized and officially approved guidelines for the quality of drugs, such as active pharmaceutical ingredients, excipients, and dosage forms. These standards are intended for use by healthcare professionals, patients, and consumers [18].

Mandate

- Publication of new editions and addendums of the Indian Pharmacopoeia
- Publication of the National Formulary of India (NFI).
- Certification and distribution of IP Reference Substances.
- Serve as a National Coordination Centre (NCC) for running Pharmacovigilance Programme of India (PvPI).
- Foster collaborative partnerships with similar institutions both nationally and internationally.
- To coordinate educational programs, skills development initiatives, and research activities, fostering a collaborative environment for growth and innovation [19].

Status of Veterinary Products Standards

A pharmacopoeial monograph provides a reliable framework for conducting an impartial assessment of the quality of a pharmaceutical substance. IP 1996, its Addendum 2000, Supplement 2000 for Veterinary Products and Addendum 2002 were developed because of the ongoing and fast expansion of the variety of pharmaceuticals produced in India. With the veterinary supplement 2000 to IP 1996, veterinary items were highlighted for the first time. For ease of access, a distinct volume of veterinary items was introduced in IP 2014.

Global Market Status of Veterinary Vaccines

Veterinary immunizations improve overall productivity and guarantee animal health in livestock farming. To meet the needs of an anticipated global population of 9.1 billion people, it is predicted that total food production will have to expand by 70% from 2005 to 2050. Vaccinations that protect animal health and increase supply are essential elements in achieving this goal [20]. The increased demand for efficient immunization solutions and the increasing frequency of various infectious epizootic diseases are the two main factors driving the global market for veterinary vaccines. Along these lines, substantial government investments in the pharmaceutical industry to improve cutting-edge production techniques for veterinary

vaccines are acting as another growth-inducing factor. The growing demand for veterinary vaccinations to stop the spread of disease-carrying bacteria from livestock-based goods, such as milk, meat, leather, eggs, and wool, is also propelling the market's expansion. Other elements, such as major advancements in healthcare infrastructure, ongoing R&D initiatives and strategic alliances amongst leading players to improve the effectiveness of veterinary vaccinations, are fostering an optimistic outlook for the market [21].

The market for animal and veterinary vaccines, which was valued at $ 10.69 billion in 2022, is projected to grow to $ 18.23 billion by 2030, with a CAGR of 6.9% from 2023 to 2030.

Some of the most common veterinary vaccinations are those against rabies, foot and mouth disease, and the equine influenza virus, which function by reproducing naturally acquired immunity to stop the spread [22]. In 2022, North America dominated the global market for veterinary vaccinations. The market for veterinary vac-

cinations was second largest in the Asia-Pacific region. Western Europe, Asia-Pacific, North America, Eastern Europe, South America, the Middle East, and Africa are the regions included in the veterinary vaccinations study. The 12 nations covered by the veterinary vaccines market include nations such as France, Germany, India, Indonesia, Japan, Australia, Brazil, China, Russia, South Korea, the United Kingdom, and the United States [23]. According to market research data, the Indian animal vaccination market is expected to reach $232 million by 2026. Given the increase in the prevalence of various animal diseases caused by the significant expansion of the poultry and animal industries, the rise of pet ownership, the adoption of scientific husbandry procedures in the large animal industry, and numerous government-led initiatives to improve animal husbandry and health, it is imperative that vaccine development continue. There is already and will continue to be a significant demand for animal vaccines as a result of these changes. More crucially the government of India's new strategy for animal husbandry and animal health requires a vigorous and broad vaccination program for livestock animals to immunize against diseases like Brucellosis and Foot & Mouth Disease (FMD). Government-run programs have also given animal vaccine producers a boost. Government funding and subsidies for the development of veterinary vaccines will be an additional benefit of this massive One Health initiative. In conclusion, it will be important to keep an eye on the market for animal vaccines. Animal immunization will be required everywhere in the world as new animal diseases endanger the future of our planet. For the successful implementation of One Health and the sustainability of our planet, urgent issues must be addressed quickly and sustainably [24].

Status of Veterinary Products Monographs

An individual volume specifically for veterinary monographs has been created as Volume IV of the 9th edition of the Indian Pharmacopoeia in order to give individuals responsible with the quality control of veterinary medicines extensive information. This volume includes a variety of chemical monographs as well as monographs on surgical supplies, diagnostic tools, and veterinary vaccines. IP 2022 volume IV comprises standards for following- General notices, Veterinary general monographs (Intramammary infusions, intrauterine preparations, Veterinary diagnostics, Veterinary immunosera, Veterinary liquid preparation for cutaneous applications, Veterinary oral liquid, oral pastes, oral powders, parental preparations, tablets and boluses, Veterinary vaccines: General Requirements), Veterinary dosage forms, drug substances, and pharmaceutical aid monographs, Veterinary biological monographs, Veterinary diagnostic monograph, Veterinary Immunosera monographs, and Veterinary surgical immunographs. The commission has also asked stakeholders to provide feedback at regular time intervals on these veterinary monographs.

A few monographs and common chapters have moreover been changed, in addition, to overhaul them as per current worldwide prerequisites and to harmonize with other pharmacopoeias like USP, BP, EP, etc. [25]. Whereas the immunizations for veterinary utilize is experiencing harmonization and are beneath talk with specialists and stakeholders. The harmonization of benchmarks with worldwide measures is anticipated to offer assistance IP getting recognized and acknowledged in outside nations. At the show, IP is acknowledged and recognized in Afghanistan, Ghana, Mauritius, Nepal, and presently Suriname. Afghanistan was the first nation to recognize IP [26]. The IP guidelines are lawfully enforceable and definitive. It is a command for drugs manufactured and showcased in India to follow to the measures endorsed in the IP, disappointment that may render the sedate not of standard quality and may result in punishments under the Drugs and Makeup Act.

Status of Veterinary Vaccines Standards in IP 2022

The Veterinary Biological Monograph in IP 2022, Vol. 4, consists of 50 veterinary vaccine monographs (Figure 1).

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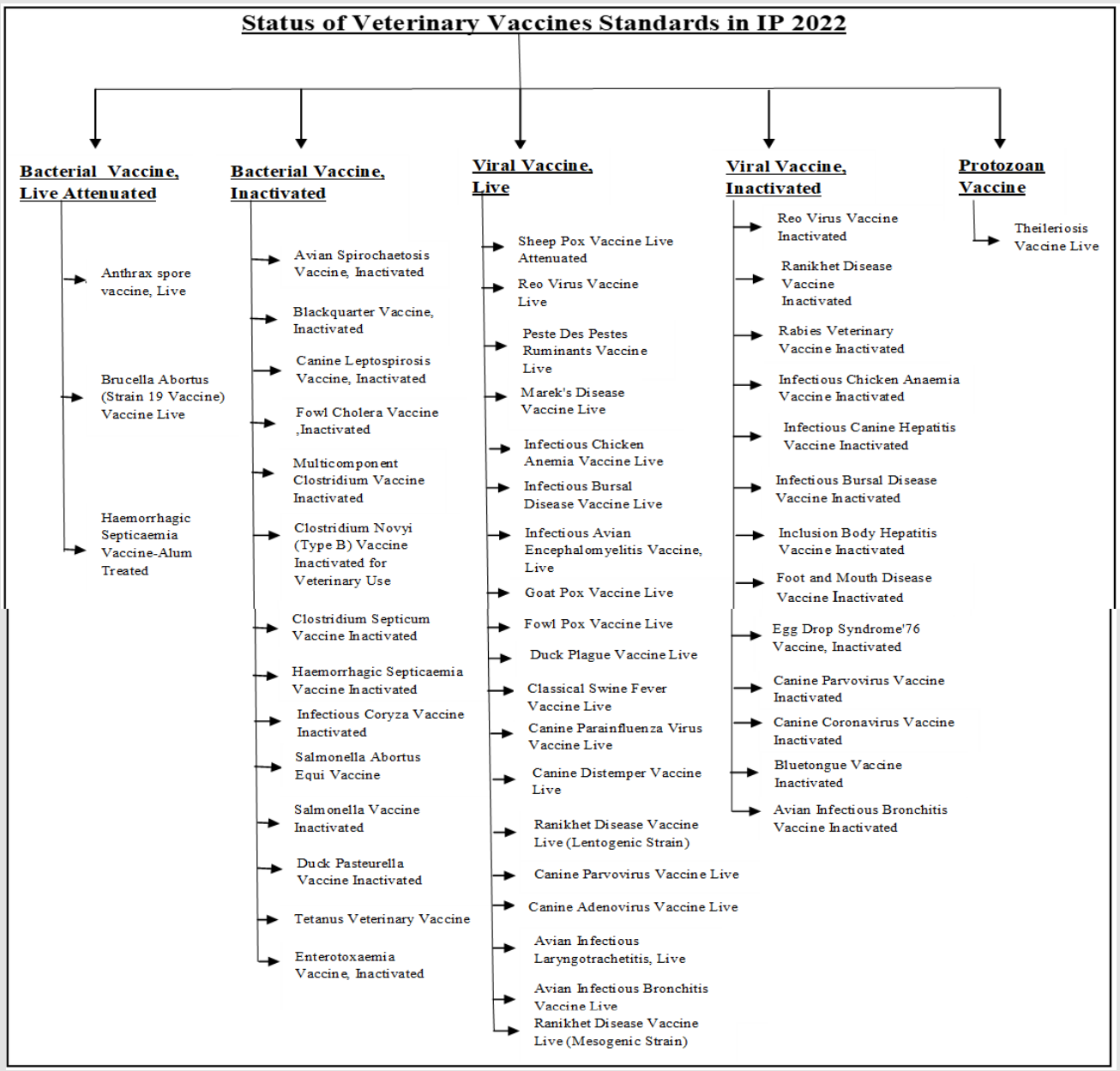

Figure 1: Status of Veterinary Vaccine Standards in IP 2022.

Need for Harmonization

The responsibility of the Pharmacopoeia is to establish or guarantee the quality of pharmaceutical standards. Quality standards (drug quality, safety, and efficacy) are crucial in the context of marketing authorization and market surveillance to ensure quality & safe standards to protect public health and facilitate the free movement and commerce of medicines between nations and regions. Therefore, the necessity for developing global quality standards for drugs, which ultimately aim at harmonizing the pharmacopoeia, is expanding as a result of globalization and the expansion of international trade [27]. The need to create global quality standards for pharmaceuticals is increasing as a result of globalization and the increase in international trade. Synchronization of standards, requirements, and regulations is crucial for international trade. Harmonization enables companies to take advantage of the essential needs of global markets, facilitating the production of market-specific products. Numerous public, private, and government entities are actively involved in harmonizing standards. Companies expanding into new markets and countries witnessing economic growth stand to benefit financially from these collaborative efforts [28,29].

Harmonization is needed since pharmacopoeial standards are an essential tool for marketing authorization, market surveillance, and the free flow of medicines between regions and nations. The advantages of establishing international pharmacopoeia standards to ensure consistent pharmaceutical quality appear evident. Currently, the bio-pharmaceutical business has a globalised manufacturing and supply chain. Having uniform standards to adhere has advantages for the industry. It is advantageous for regulators to be able to examine drug applications and pharmaceutical facilities anywhere without being hindered by inconsistent pharmacopoeia standards. Most importantly, there is a worldwide patient population today. Patients all over the world will ultimately benefit from being able to access medicines that are of the same quality, assessed against uniform standards found in all pharmacopoeias, regardless of where the product or its components were made [30]. Need for Pharmacopoeial Harmonization-

- The purpose of creating a drug product that can satisfy the various market requirements is to develop
- By eliminating duplication of effort, we reduce the overall cost of pharmaceutical research globally.
- Update of the monographs with new Science and Technology inputs
- As a result, cutting down on the time required for a) the availability of new medicines, b) the maintenance of international quality standards for marketed drugs (life cycle maintenance of marketed medicinal products), and c) the broadening of established medications to various regions (as part of the geographical expansion of medicinal products)

The Indian Pharmacopoeia Commission understands the value of collaborating with other pharmacopoeial bodies to provide uniform general chapters and monographs. The streamlining and rationalization of quality control systems and licensing procedures are just two advantages of this harmonization, which is completely aligned with the Commission's stated goals. Since some of the developed guidelines rely on pharmacopoeial general chapters for their application, such harmonization also increases the advantages of the work of ICH and VICH. The restructuring of the monographs has been undertaken for the following reasons.

- The up gradation of these monographs is required to meet global requirements.
- There is a lack of uniformity within the IP monographs.
- Restructuring of monographs along with harmonization with international standards helps in increased globalisation of domestic products.

Development of Restructured Veterinary Vaccine Monograph

(Figure 2).

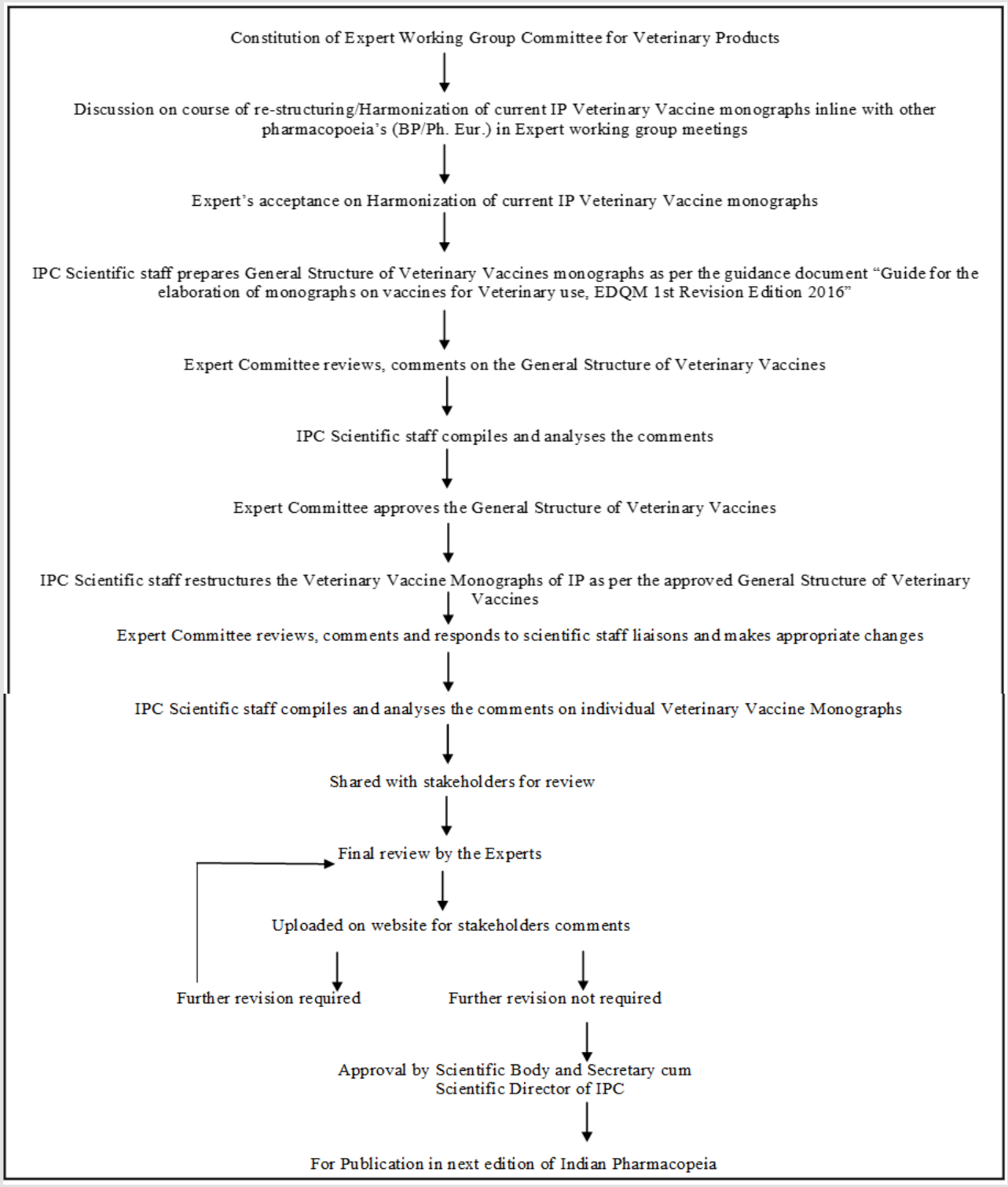

Figure 2: Process of Restructuring Veterinary Vaccine Monograph.

Background of the Structure for Veterinary Vaccines in IP

Purpose of the Structure of the Veterinary Vacuum

This structure guide provides guidance to contributors of Indian Pharmacopoeia monographs on veterinary vaccines. The aforementioned applies specifically to the

1. Group of experts and higher approval authorities for vaccines for veterinary use.

2. The National Control Laboratory (NCL) is also subject to these provisions.

3. Manufacturers of vaccines and immunosera for veterinary use are also included in this category.

4. Additionally, analytical laboratories (both public and private) that work for any of the entities mentioned above are also covered by these regulations [29].

The official standards for medicinal products are established by the monographs and general chapters of the Indian Pharmacopoeia. Should there be any uncertainty or disagreement, the Indian Pharmacopoeia text holds the ultimate authority (Figures 3-6).

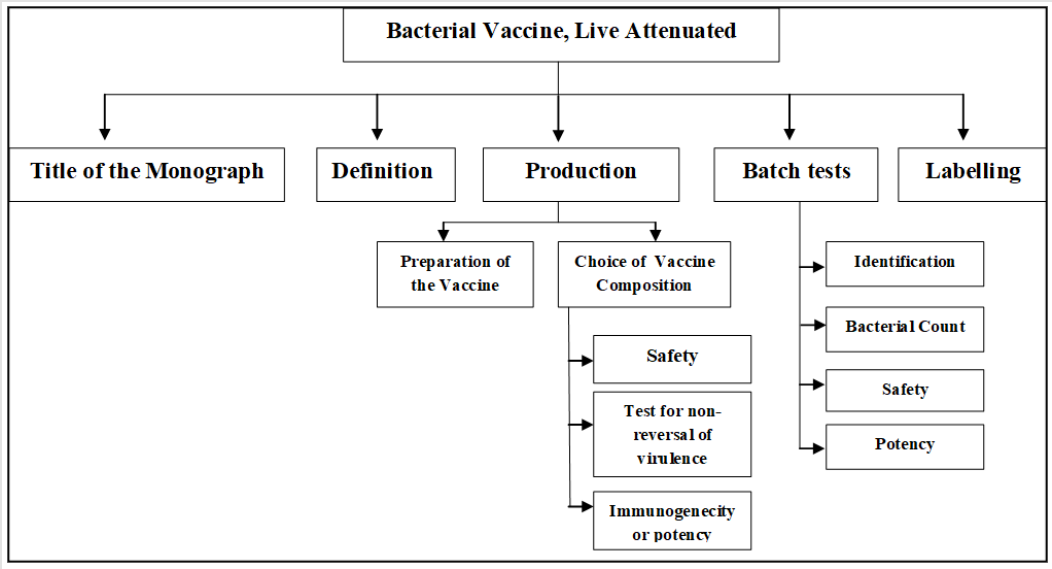

Figure 3: Structure of Bacterial vaccine, live attenuated for veterinary use monographs in IP 2022.

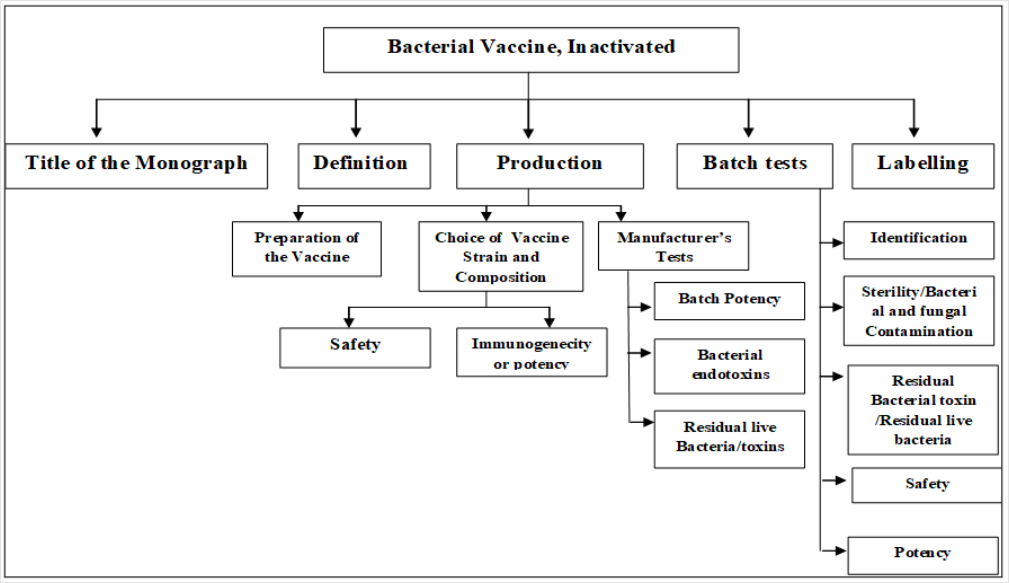

Figure 4: Structure of Bacterial vaccine, inactivated for veterinary use monographs in IP 2022.

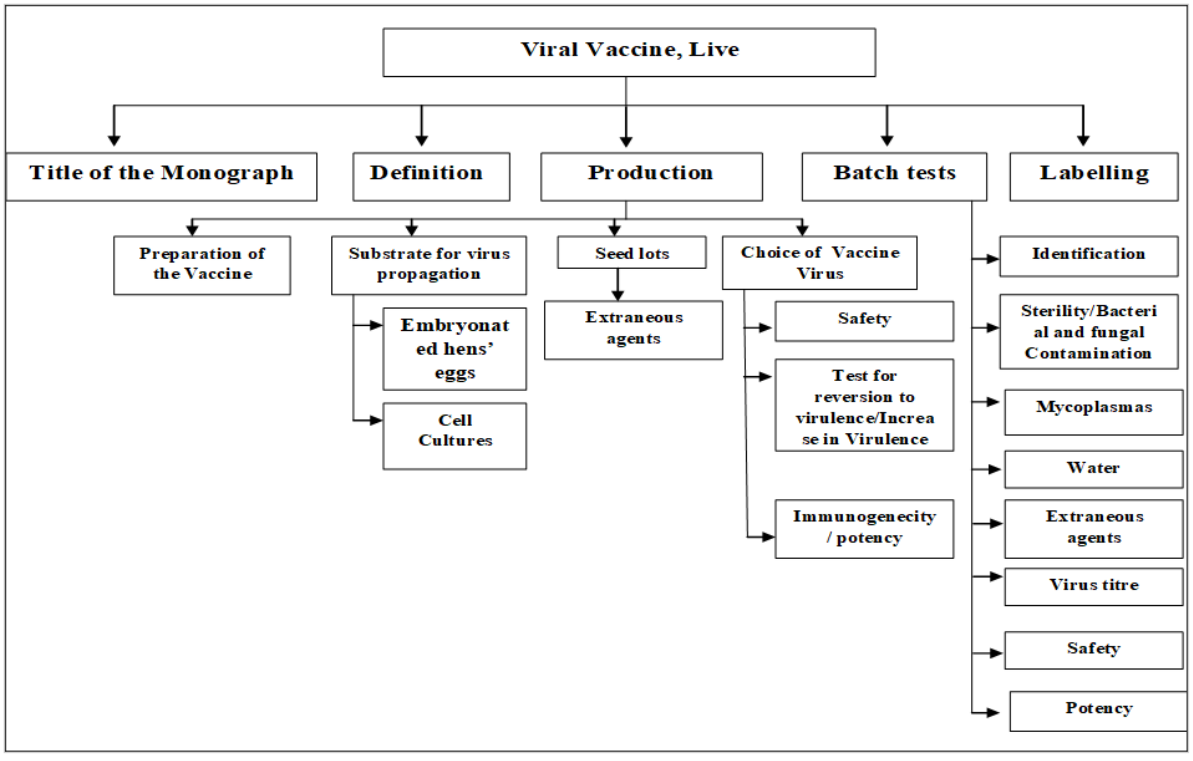

Figure 5: Structure of the viral vaccine, live for veterinary use monographs in IP 2022.

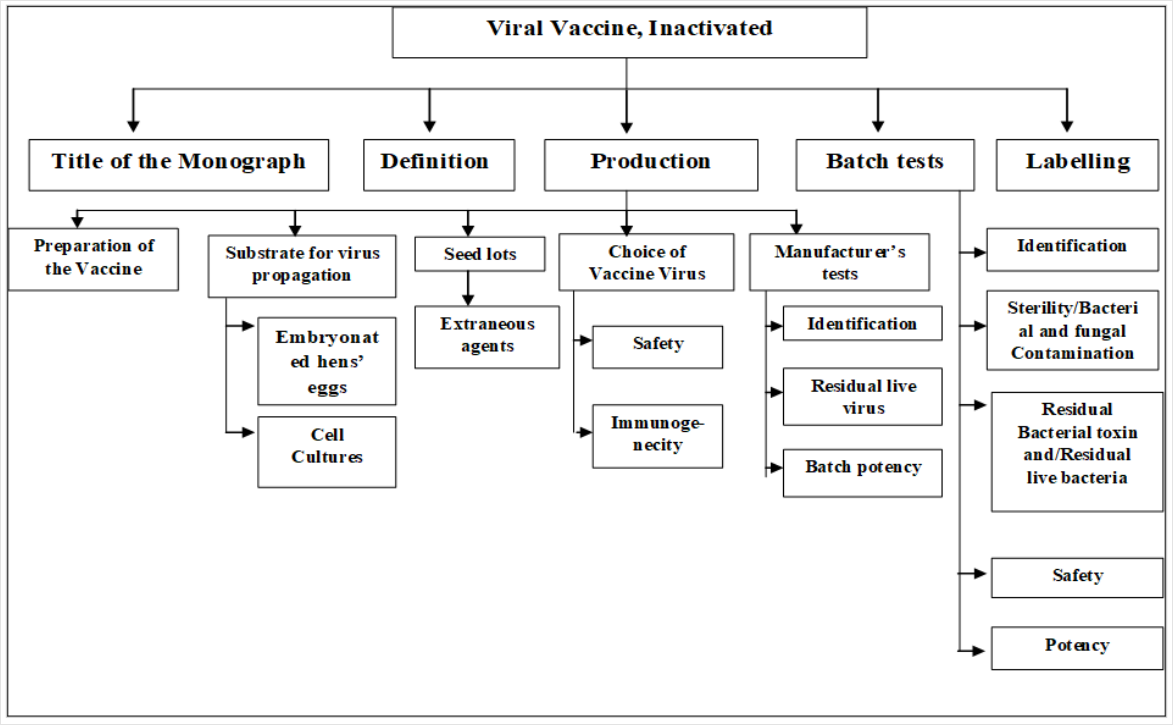

Figure 6: Structure of viral vaccine, inactivated for veterinary use monographs in IP 2022.

Content of the Monographs on Vaccines for Veterinary Use

The General Notices state: "All statements contained in the monograph, except where a specific general notice indicates otherwise and with the exceptions given here after, constitute standards for the official articles. Exceptions to the General Notices do exist, and where they do, the wording in the individual monograph or an appendix takes precedence and specifically indicates directions or the intent. Thus, the specific wording of standards, tests, assays, and other specifications is binding wherever deviations from the General Notices exist. Likewise, where there is no specific mention to the contrary, the General Notices apply" [16]. The requirements for a particular preparation may not be fully comprehensive; additional requirements could be specified in the individual monograph. Drug products covered in an individual monograph must also meet the tests described in general monographs. The drug products specified in an individual monograph must also meet the requirements set forth in the general monographs.

Sections of the Monographs

The restructured IP monographs are designed under the following sections.

Title of the Monograph: The title of the monograph consists of

1. Vaccine and the type i.e. live or inactivated
2. Name of the disease for which it will be used
3. 'for veterinary use' (where the vaccine for human use also exists) should also be mentioned, and
4. the target species where necessary, for example. Brucella Abortus (S19 Vaccine) Vaccine, Live, Canine Adenovirus Vaccine, Inactivated
5. Synonym of the vaccine.

Definition: The monograph outlines the extent of its coverage and its significance for the products accessible on the market. It establishes the authoritative reference point for all products falling under this description. Furthermore, the product composition is succinctly detailed in each individual monograph. For example, a vaccine (live / inactivated) is a formulation of one or more appropriate strains [bacteria / virus]. This monograph is applicable to vaccines designed for active immunization (Live Vaccines) or those that are inactivated but retain sufficient immunogenic properties (inactivated vaccines).

Production: The content of this section is primarily directed towards manufacturers. The document covers the principles and details related to vaccine production, the anticipated tests throughout the product's creation, the regular and ongoing tests that producers may perform, and the batch tests executed to guarantee the pharmaceutical quality of the product. Manufacturers are provided with direction on how to demonstrate the clinical value and efficacy of their products through developmental testing. The production section of the general and individual monographs contains a blend of requirements and information related to specific aspects of the manufacturing process, such as source materials, process validation and control, and in-process testing. These elements are crucial in showcasing the consistency of the manufacturing process.

This subsection in the individual monograph includes specific requirements for:

- Preparation of the Vaccine: This subsection discusses the various techniques used in the vaccine preparation, including the propagation and harvest of bacterial and viral antigens, the inactivation process, and the preparation of the final bulk and batch. The production of the vaccine is based on a seedlot system, which ensures consistent and reliable manufacturing. For inactivated bacterial vaccines, the seed lot is cultured in a suitable medium to promote optimal growth under specific incubation conditions. After culture, the bacterial suspensions are collected and subsequently rendered inactive using a suitable technique. In the case of live vaccines, they can be lyophilized, liquid, or frozen. The formulation may also include stabilizers, buffers, excipients, and an adjuvant to enhance its effectiveness. The vaccine virus is typically grown in embryonated hens' eggs or in cell culture.

- Substrate for Virus Propogation: Embryonic eggs. The eggs of the embryonated hens are sourced from SPF flocks when the vaccine virus is cultivated in them. Cell cultures. Alternatively, cell cultures must meet the standards for the production of veterinary vaccines if used for virus growth. In the case of continuous cell lines, they must originate from a seed-lot system. When primary chicken cells are used, they should come from SPF flocks.

- Seed Lots

a. Extraneous Agents

The master seed lot satisfies the criteria for the presence of foreign agents in the seed lots. It passes the test if it does not induce the production of antibodies against the agents tested. During the examination of the master seed lot, the organisms utilized are within 5 passages from the original seed lot at the start of the tests.

b. Choice of Vaccine Composition and Choice of Vaccine Strain: This section pertains to the safety and effectiveness assessments that must be performed while developing a vaccine, as outlined in Sections (2.7.17) and (2.7.12). Normally, these assessments are performed just once throughout the vaccine development process. Unless specified otherwise, the testing procedures provided for confirming these attributes and the acceptable limits, when applicable, are included as illustrative examples of suitable methods and the corresponding limits. However, developmental evaluations must be performed in a manner that ensures that the product meets pharmacopoeial standards [29].

c. Safety: Compliance with the detailed requirements specified in the chapter (Evaluation of safety in veterinary vaccines and immunosera) is essential. The individual monograph may provide technical insights into various tests to assist in establishing appropriate protocols. To assess the effectiveness of animal vaccination methods and routes of administration in all relevant categories, it is essential to carry out tests using animals that are below the minimum vaccination age.

d. Test for Reversion to Virulence/Increase in Virulence: For live vaccines, for example, details are usually provided for the conduct of the test for increase in virulence. Carry out the test using an animal / SPF flock if it is chicken free from antibodies against [virus]. The vaccine virus is in accordance with the test if there are no indications of increased virulence in the organism obtained from the final passage when compared to the material used in the first passage.

e. Immunogenicity or Potency: The administration of vaccination tests should be performed for each recommended route and method unless otherwise specified in the monograph. The age of the subjects used in the tests should not exceed or fall below the minimum or suitable age recommended for vaccination. The quantity of the vaccine strain administered to each animal should not exceed the minimum number of live bacteria stated on the label, and the strain present in a batch of vaccine should be at its most attenuated passage level. The specific procedure for testing will be defined for each individual vaccine.

Manufacturer's Tests: This segment focuses on the examinations that the manufacturer may carry out as part of the testing process to demonstrate that each batch meets the required quality standards. These tests are specifically designed to ensure that the batch complies with the pharmacopoeial requirements outlined in this section. This section covers a wide range of test variations which are tailored to the specific characteristics of the product. The tests carried out by the manufacturer, which are specific to each product, are compiled in the dedicated section of the individual monographs. There are no specific numerical limits provided, as the manufacturer needs to establish these limits based on the observed values from batches of vaccines that have been proven to be safe and effective. The most frequently listed tests in individual monographs are as follows:

- Identification: Identification of the vaccine virus is accomplished by using appropriate molecular biology, biochemistry, cell culture, and immunochemical techniques.

- Batch Potency Test: Conducting the relevant potency test or tests for every batch of the vaccine is not required if a batch with a minimum potency has already undergone the test. In the absence of these tests, an alternative validated method is utilized, with acceptance criteria determined based on a batch of vaccines that has shown satisfactory results in the potency test.

- Residual Live Virus: A test is performed to determine the presence of any remaining live viruses. The amount of inactivated virus used must be equal to or greater than x doses of vaccine. If a live virus is not detected, the inactivated virus harvest is considered to meet the test requirements. In the case of live vaccines, analysis must be performed to determine the concentration of virus or the number of bacteria as specified in the relevant individual monographs and general monographs. An appropriate acceptance criterion for this test is expected, which takes into account the following points: - The minimum acceptable virus concentration or bacterial count should be determined during development studies, based on the vaccine sets used in the efficacy test or other efficacy studies. - The loss observed in stability studies should be added to this value to ensure that the content remains above the minimum acceptable concentration or amount at the end of the shelf life. The concentration or amount equal to or greater than the calculated value must be checked after the release of each batch. For inactivated vaccines, it is assumed that instead of a potency test, an appropriate group efficacy test will be developed for routine use. Acceptance criteria must be determined on the basis of the correlation of the results of the set that passed the performance test. This information is generally presented in a comprehensive manner and may suggest different methods. For inactivated vaccines, it is recommended to consider the use of in vitro methods during development, provided that the most important in-process parameters are defined and monitored and in-process control tests and the target composition of the final product are considered.

Batch Tests: This section focuses on tests that a manufacturer can perform as part of the testing process to demonstrate that each lot meets the required quality standards. The purpose of these tests is to verify that the batch complies with the criteria outlined in the pharmacopoeia. The manufacturer's test section in individual monographs contains specific tests based on the nature of the product. It provides information on tests that must be performed regularly and can be applied to many vaccines. The general monograph section contains guidelines and qualification scores for tests such as free for maldehyde, phenol, identification, sterility, foreign body mycoplasma, safety and efficacy. The individual monographs in this section describe the tests and requirements that all product lots must meet during their shelf life. This means that all lots on the market must meet these requirements when tested by an independent analyst. In order to exempt the batch manufacturer, these tests do not need to be carried out for each batch, if the tests carried out during production or other tests on the final product provide an equal or better guarantee of conformity or if alternative tests have been validated according to the pharmacopoeial method. Except for a few cases, individual monographs consistently have a section called Power. This usually involves performing the test described in the Immunogenicity section. The monograph incorporates an efficiency test that can be conducted on any batch, thereby utilizing a single recommended method of administration.

- Identification: The vaccine strain is determined through the use of suitable methods. Eachindividual strain within the vaccine is identified through various methods such as morphological, serological, molecular, immunochemical, or biochemical techniques, along with culture on selective medium.

- Bacterial and Fungal Contamination / Sterilization (2.2.11): To evaluate the efficacy of live vaccines, it is essential to quantify the population of live bacteria in a suitable solid medium for the cultivation of bacterial strains. The vaccine is deemed compliant if each dose contains no less than the minimum number of live bacteria specified on the label. Similarly, inactivated vaccines, together with the applicable reconstitution diluent, must meet the sterility test outlined in the general requirement.

- Mycoplasmas (2.7.8 or 2.7.9): The vaccine meets the requirements for mycoplasma testing.

- Water (2.3.43) Percent Moisture Content if it is a Lyophilized Formulation.

- Extraneous Agents: For live viral vaccines, it is essential to use a monospecific antiserum to neutralize the vaccine virus before inoculating it into cell cultures that are susceptible to animal pathogens. The vaccine is deemed acceptable if there are no cytopathic effects observed and there are no haemagglutinating or haemadsorbing agents present. Furthermore, the batches of finished products undergo tests to ensure that the vaccine meets the required criteria for extraneous agents.

- Safety: Each recommended route and method of administering the vaccine to animals in relevant categories or laboratory animals should undergo testing. Animals selected for the test must be within the recommended minimum age for vaccination, as outlined in the individual monograph. The test should be conducted using an attenuation level equal to or less than the commercial batch. Furthermore, the test should be performed with the highest expected dose level or a microbial count that is [number] times higher than a single dose. When in vivo batch tests are performed on target animals for purposes other than the target animal safety test, such as potency tests, and these tests involve the collection of safety information, such as mortality data, it is recommended that manufacturers make use of these tests to gather additional safety data for the vaccine in the target species.

2. Note: General requirements shall be referred to regarding omission of the batch safety test.

- Potency: The vaccine meets the requirements of the immunogenicity test when administered by the recommended route and method. It is not necessary to conduct the potency test for every batch of vaccine if it has already been performed on a representative batch using a vaccine dose that contains no more than the minimum bacterial count indicated on the label. An alternative in vitro method can be utilized as a potency test for batch release if a correlation between the potency test and the alternative test has been established. In the batch test, the virus titer can be used as a substitute for in vivo potency testing if a correlation between the virus titer and potency has been established [31].

Labelling: The labeling requirements outlined in the general monograph are applicable to all veterinary vaccines. Additional information may be required for specific vaccines, which will be incorporated in the individual monograph in the Labeling section. This supplemental information complements the general requirements of the monograph. The label must clearly indicate that the vaccine is 1. for veterinary use only, 2. the recommended routes of administration, 3. instructions for use, 4. the targeted animal species, 5. storage temperatures, 6. Batch Number, Manufacturing date, date of expiry, 7. precautions for pregnant animals, 8. total volume and number of doses, and 9. a statement in compliance with the approval document [29].

Major Highlights of Restructuring

Indian Pharmacopoeia Commission (IPC) has taken initiatives to implement 3R through the Indian Pharmacopoeia (IP). Through deletion of animal tests at final lot for biologicals and scope of reduction in number of animals used where deletion of the animal test is not possible and refining the tests causing the minimum suffering to the animals are explored.

Target Animal Batch Safety Test

Blanket waive off for all vaccines may have a risk involved considering the fact of potential safety risk involved. Therefore, the provision for conditional waiver for the target animal batch safety test is included in all veterinary vaccine monographs and general requirements for veterinary vaccines along with a note are included in the revised 'General requirement-Veterinary vaccines' for the waiver of TABST. Note: The batch safety test using target animal can be omitted if 1] safety test has been performed with satisfactory results in the master seed lot and 2] the consistency of the manufacturing process has been well established to the satisfaction of the National Regulatory Authority and 3] at least 10 consecutive production batches have been produced and comply with the safety test. Significant changes to the manufacturing process may require resumption of routine safety testing to reestablish consistency.

Batch Potency

Hemorrhagic Septicemia Vaccine, Inactivated: For batch test, mice potency test will be included in addition to cattle as was mentioned earlier in IP 2010 & IP 2014.

Immunogenicity

Along with sheep, a laboratory model (guinea pig or rabbit) is also included as a model for the immunogenicity testing under production.

Safety

Canine parvovirus, activated - reduction in the number of target animals, ie, dogs, from six to two in the safety test under production.

Challenges While Harmonizing the IP Veterinary Vaccine Monographs

Pharmacopoeial harmonization assists global patients who depend on these medications to prolong and improve their lives by improving support for international regulatory organizations and addressing the global nature of bio-/pharmaceutical manufacturing and delivery. In addition, there are still several obstacles in the way of the total harmonization of these IP monographs. First, the safety profiles and therapeutic efficacy of finished pharmaceutical products (FPPs) are greatly influenced by their quality. Production is becoming more multi-national because of global trade and pharmaceutical firm mergers, which upset national restrictions. However, the failure to follow Good Manufacturing Practices by manufacturers and ineffective quality control measures may result in quality faults. Although various manufacturers may use various control mechanisms, experience has shown that some quality control and manufacturing procedures are insufficient to guarantee the creation of high quality medications. Despite the various measures implemented to address these deficiencies, additional rigorous protections must be established. However, it should be noted that more stringent regulations could lead to higher expenses and additional challenges for both producers and regulators, who are already facing resource constraints. Second, there is diversity among the antigen strains found locally. Since antigenically variable pathogens (AVPs) are the primary cause of infectious diseases today, they bear a heavy cost. The biggest challenge in creating new or better vaccines is high genetic and antigenic heterogeneity. In addition, there is a growing public awareness of the positive impacts of veterinary vaccines on animal health. Ultimately, if vaccines are to be used, they must be produced in such a way as to ensure consistent and high-quality performance. Since vaccines are those biological products that exhibit intrinsic variability and therefore, again making this harmonization challenging at the grass root level [30].

Conclusion

The Indian Pharmacopoeia (IP) is the official document defining the standards for drugs in India and contains detailed information on the quality, purity, and potency of medicines available in the country. The role it plays is essential to guarantee the quality, safety, and effectiveness of medications in India and is an important tool for the pharmaceutical industry, regulatory authorities, and healthcare professionals. Pharmacopoeial standards are an essential cog in the proper operation of marketing authorization and market surveillance processes, as well as the free movement and commerce of drugs worldwide. Harmonization of global pharmacopoeia would improve access to high-quality pharmaceuticals for people all over the world. These continuous harmonization efforts are supported by the industry's position on the ideal pharmacopoeia and methods for achieving compendial globalisation. The industry benefits from having consistent standards with which to comply. Regulators gain from the ability to assess drug applications and visit pharmaceutical facilities anywhere, without the complications of various pharmacopoeia standards. Most importantly, the patient population today is global. Finally, patients around the world will benefit from receiving medications of the same quality, measured against standard requirements included in all pharmacopoeias, regardless of where the product or its ingredients were created.

Data Availability

The research data is not presented in the article.

Declaration of Conflicting Interests

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