Biomanufacturing of vaccines. A narrative review

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Narrative Review

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Abstract.
Background.The manufacture of vaccines is a process that is supervised and continuously evaluated by regulatory authorities through compliance with good manufacturing practices, to support their safety and efficacy, and to ensure that they can be used in humans, which must meet high quality standards, both at the level of the active substance and the finished product. Likewise, the plants where all manufacturing processes are carried out must comply with the requirements of Good Manufacturing Practices (GMP), according to the World Health Organization (WHO).

Objectives. To understand the processes of manufacture of antigenic substances according to the types of vaccines and to describe the characteristics of the facilities of a vaccine biomanufacturing plant. Method. The methodology used for the review was a search for scientific articles and literature in the search engines PubMed, Cochrane, Google Scholar and Preprints, focused on vaccine Biomanufacturing.

Discussion. The World Health Organization (WHO) and medicines regulatory agencies establish a series of standards or instructions for obtaining antigens for vaccines in the different platforms, as well as for the plants where the final manufacture is carried out, in addition to the formulation and quality control components necessary to provide safe and effective vaccines to patients.

Conclusions. Vaccine biomanufacturing is a process of utmost importance for public health systems, since immunization saves many lives around the world, reduces the cost of care for current and emerging diseases, and contributes to the fight against antimicrobial resistance.

Key words: Vaccine, Upstream, Downstream, Biomanufacturing, Biomanufacturing plant

Introduction

Vaccines are one of the most effective public health intervention tools for disease control, based on evidence obtained from the clinical phases of development, such as preclinical studies, phase I, II and III studies. According to current statistics, they save around four million people a year, managing to extend the life expectancy of people who are immunized for longer and in a healthier way (Government of Canada, 2024).

Vaccines are preparations containing antigens capable of inducing specific and active immunity in humans against an infectious agent, or the toxin or antigen produced by it Spanish Agency for Medicines and Medical Devices (by its acronym in Spanish AEMPS), 2024). The therapy causes the immune system to generate antibodies through the induction of the innate and adaptive mechanisms of the immune system, simulating exposure to

a specific pathogen, without causing the disease characteristic of the bacteria or viruses it contains, either completely, but dead or attenuated; as well as fragments thereof or their antigens, in such a way that the risk of inducing serious complications in the people to whom they are administered is reduced (World Health Organization (WHO), n.d.).

The vaccine manufacturing process is complex and is divided into two major stages, each with well-defined steps to follow during its execution: Upstream, the first stage where the culture and remanufacture of cells with the antigen or protein of interest is carried out, under controlled storage conditions, temperature, aeration, pH and nutrients, to obtain adequate and comparable results; Downstream, the second stage in the Biomanufacturing flow, where purification activities are carried out, obtaining the active substance in bulk, free of contaminants, to later proceed to the formulation, adding excipients necessary for the stability and administration of the vaccine. Likewise, the facilities of the manufacture plants must be designed and adapted to achieve the objective of each of the stages of vaccine development, in such a way that it is efficient and with quality products. For this reason, during the design and manufacture of the active substance as well as the finished product, a series of guidelines, standards and guidelines that govern the application of Good Manufacturing Practices must be followed, established to guarantee the quality of vaccines intended for human consumption, complying with specifications of identity, concentration, purity and potency (Gómez et al, 2013).

The objectives of this review have been to identify the manufacture processes of antigenic substances according to the type of vaccine, as well as to describe the characteristics of the facilities of a biological drug manufacturing plant with respect to a drug manufacturing plant.

Methodology

A narrative review of scientific articles and literature available in search engines such as PubMed, Cochrane, Google Scholar and grey literature from preprints dealing with the topic "Biomanufacturing of vaccines" was conducted. The search was conducted using the keywords "Biomanufacturing", "upstream", "downstream" and "biomanufacturing plant". Publications (regulations, guidelines, regulations and books in general) from regulatory entities, as well as reference institutions in the field, were also included. The selection of the through complete reading, thus determining their usefulness for the fulfillment of the proposed objectives.

Discussion.

Vaccines are a vital method of protection against diseases and one of the greatest advances in public health (Unicef, n.d.). Immunization has saved many lives around the world. Its main mechanism of action is through the activation of the immune system, forming antibodies that react to diseases or pathogenic microorganisms that cause serious infections (Reyes González, 2022). Likewise, they have a positive economic impact on all health systems.

Preclinical and clinical development of vaccines.

Vaccines are thoroughly evaluated by reviewing all preclinical and clinical laboratory data to verify safety, efficacy, purity and potency. Vaccines that are approved by regulatory agencies for sale to the public are often asked to submit additional studies that allow for a thorough evaluation of the vaccine, in order to resolve doubts that arise during the evaluation about the safety, efficacy or possible side effects of the vaccine (Gómez et al, 2013).

Before vaccines can be applied in human beings, they are evaluated through preclinical studies, which can be in laboratory animals such as monkeys, mice or in cells produced in the same laboratory for this purpose, with the objective to verify the safety and, in addition, to evaluate if it is capable of generating an immune response.

This type of trial serves to determine safe doses and to begin testing in human beings, since with the results obtained, the researchers make the decision to modify or improve the vaccine. Those that do not produce sufficient immune responses to prevent the target disease, do not continue to the next phase of developing.

The research phases in human beings include clinical trials phase I, II and III (Public Health Institute, ISP by its acronym in Spanish, n.d.).

Phase I. Clinical trials in which the vaccine in development is evaluated for the first time in human beings, the number of subjects receiving the intervention is small, between 20 to 80 people. The objectives of this phase are: to verify safety and tolerance, as well as the immunological response and efficacy.

Phase II. At this stage of vaccine development, the number of subjects who are tested is greater, between 100 to 500 subjects, verifying the antigens immunogenicity and safety. This stage is important since it is where the dose, the application time between doses, as well as the route of administration are established.

Phase III. In phase III clinical trials, the number of subjects receiving the intervention is much greater, there may be thousands of people participating. At this stage, the aim is to determine efficacy and safety of the active antigen formulation. This stage is very important because it is where expected or common adverse events can be identified.

Development of the active substance

The manufacture of vaccines is a complex process made up of different stages, which require many controls, through which safe and quality active substances are obtained; in vaccines, the active substances are called antigens (Government of Canada, 2022), or protein molecules that entering the human body provoke an immune response, since the immune system detects them as foreign agents, triggering the manufacture of antibodies that bind to the antigen until it is neutralize it. If in the future the microorganism carrying the antigen against which the immunization has been carried out enters the body, the antibodies generated by the vaccine will be able to protect the body, preventing the development of the disease, or at least, part of the symptoms that this microorganism causes.

Currently, vaccines development and manufacture methods have diversified due to advances in science and technology, these can vary depending on the type of antigen to be obtained and the starting materials used, grouped into technological development platforms, according to source of the National Centre for Immunization Research Surveillance NCIRS, April 2023:

- Whole agent: live, attenuated or weakened viruses or bacteria that do not cause disease, but induce the desired immune response; or inactivated by chemical or physical agents.
- Proteins: such as component subunits of the antigen of interest or virus-like particles.
- Viral vectors: harmless viruses modified to incorporate the genes that encode the antigen of interest and enter them into human cells for endogenous manufacture of the antigen. These modifications do not allow them to multiply or integrate into the host genome.
- Nucleic acids: genetic material that is introduced into human cells, said sequences specifically encode the antigens of interest for their endogenous manufacture (World Health Organization (WHO), n.d.).

Whole virus or bacteria vaccines

Inactivated vaccines. This is one of the first strategies used for vaccine manufacture, whose importance prevails today, being one of the most used methods for vaccine manufacture, since it has been shown to work to treat diseases that affect many people (influenza vaccine, polio vaccine, among others), and allows manufacturing on a large scale, since inactivation is carried out by means of chemical substances, heat or radiation (World Health Organization (WHO), n.d.).

Attenuated vaccines

To produce this type of vaccine, pathogenic viruses that are still active are used, but which are weakened in order to reduce their capacity to cause the disease or its severe stages. It should be noted that the technology used in this group of vaccines is very similar to that of inactivated vaccines (World Health Organization (WHO), n.d.).
Viral vector-based vaccines. Harmless viruses are used to manufacture this type of vaccine. These viruses are capable of transporting a specific fragment of the pathogenic virus of interest so that an immune response can be produced, but which does not cause the disease. They contain the information to reproduce the specific fragments, functioning as a vector through which the fragment of interest is introduced into organisms (World Health Organization (WHO), n.d.).

Vaccines that use antigenic subunits

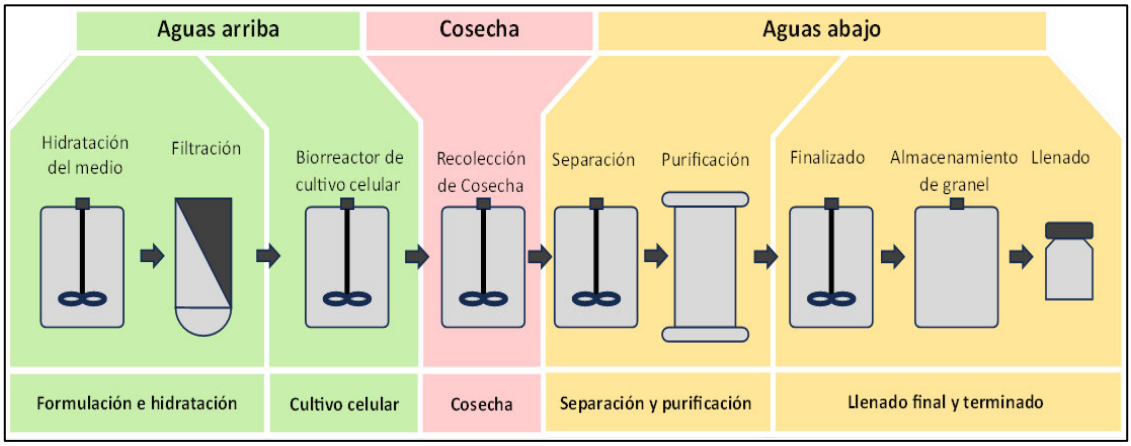
This type of vaccine uses the antigenic subunit, which are specific fragments of the pathogen of interest. The subunit can be a protein or sometimes carbohydrates (World Health Organization (WHO), n.d.).

Vaccines manufactured from genetic material or nucleic acid. This type of technology is one of the newest for vaccine manufacture. In this class of vaccines, only a sequence of genetic material is used, which provides the information for the manufacture of the proteins of interest (World Health Organization (WHO), n.d.).

The manufacturing process involves two processes: upstream and downstream.
Upstream and Downstream processes.

The manufacture of biological, biotechnological and vaccines products represents one of the most significant contributions in modern medicine. This process includes several fundamental stages, usually separated into two phases: upper and lower. Each phase has a crucial impact on the quality, safety and efficacy of the final products (Venair, n.d.), see figure 1.

Figure 1: Bioprocess flow diagram



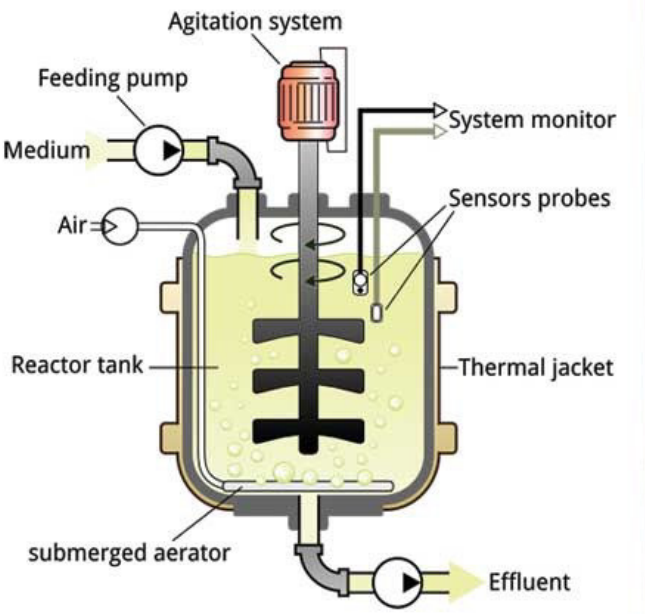
Source: taken from Collegedunia, bioprocessing, cellular bioprocessing, upstream and downstream. https://collegedunia.com/exams/bioprocessing-biology-articleid-3817

Upstream Processes
Upstream procedures constitute the beginning of biological manufacturing and focus on the generation of cells that will produce the active component of the drug. This phase includes the selection of the correct cell strain, the conditioning of the culture media and the growth conditions, essential elements to ensure optimal performance (Gallardo J., n.d.).

1. Cell Selection: The choice of cell system is critical to the success of the manufacturing process. Manufacture systems may include:
a.Bacteria: E. coli is usually handled due to its rapid growth and easy genetic management, although it lacks the capacity to perform post-translational modifications (Gallardo J., n.d.).
b.Yeasts: These provide a balance between growth speed and ability to perform certain post-translational modifications (Gallardo J., n.d.).
c.Mammalian cells: They are used in proteins that require complex modifications, such as glycosylation, which are essential for biological activity (Gallardo J., n.d.).

2. Culture conditions: Optimization of culture conditions is crucial. This includes medium formulation, pH regulation, temperature and agitation of the bioreactor, see figure 2. Automated control and real-time monitoring techniques are revolutionizing this phase, allowing immediate adjustments to maximize cell yield (Reyes L, n.d.).

Figure 2: Bioreactor o Fermenter



Source: – Labster, (n.d

3. Process validation: Validation is essential to ensure that each stage produces a product that meets the required specifications. This involves testing to verify the stability and productivity of the strains used. The ability to scale up the process from a laboratory to an industrial manufacture plant requires a thorough understanding of cell culture dynamics (Walsh, 2013).

4. Challenges in scalability: Transitioning from small facilities to large-scale manufacture presents unique challenges. It is vital that laboratory conditions are effectively replicated in larger bioreactors. This may involve implementing mathematical models and simulations to predict how cells will behave under different conditions (Fahnert B., et al. 2012).

Downstream process

The downstream process begins once the active ingredient has been produced. This stage includes purification, formulation and quality control of the product. This process is essential to ensure that the final medicine is safe and effective (Venair n.d.).

1. Purification:: Purification of the biological product is a critical step that is carried out using a variety of techniques. These may include:

a. Centrifugation: to separate dead cells and other solids from the liquid.

b. Filtration: to remove smaller particles that may be present.

c. Chromatography: este es un método común que se utiliza para separar proteínas basadas en sus características específicas, como tamaño, carga o afinidad. La cromatografía de afinidad, en particular, permite una separación altamente específica que es vital para la calidad del producto final (Janson, J, 2011).

2. Formulation: Product formulation is the next critical step. This phase involves the addition of excipients, stabilizers, and preservatives that help maintain the integrity of the product during storage and use. Immunogenicity is especially relevant in the case of vaccines, where the patient is immune response is critical (Boulanger, P., et al, 2014).

3. Quality Control: Biologics must undergo rigorous quality control to verify their purity, potency, and safety. This includes testing for stability, toxicity, and efficacy before they are released for commercial use. High-vigilance regulatory agencies set strict standards that must be met, ensuring that products are safe for the population.

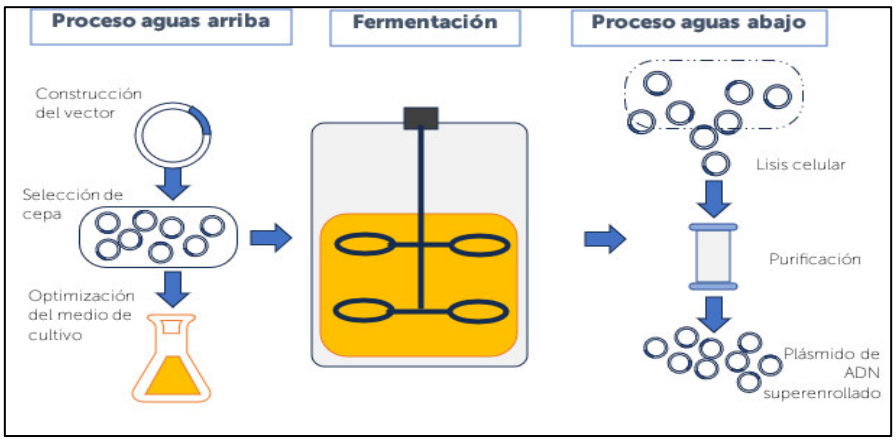
Integration of Upstream and Downstream Processes

Upstream and downstream processes (see figure 3) are essential for manufacture efficiency and quality. A holistic approach allows manufacturers to identify areas for improvement and optimize each stage of the process. The use of emerging technologies, such as artificial intelligence and data analytics, can facilitate this integration, allowing for better management of resources and increased productivity.

1. Monitoring and automation: The implementation of real-time monitoring and automation technologies in biomanufacturing is transforming the industry. These technologies allow for instant adjustments to culture and purification conditions, improving product quality and reducing manufacture time.

2. Research and Development: Ongoing research in biotechnology is leading to the creation of new manufacture and purification methods, as well as improved formulations. The development of new expression platforms and purification technologies can reduce costs and increase efficiency.

Figure 3: Bioprocess flow diagram



Fuente: tomado de Collegedunia, bioprocesamiento, bioprocesamiento celular, ascendente y descendente. https://collegedunia.com/exams/bioprocessing-biology-articleid-3817

Formulation

After obtaining the antigen of interest, the vaccine moves on to the formulation stage, in which excipients are added to form a mixture that can guarantee the stability, efficacy and safety of the vaccine, as well as its potency over time. Today there is a variety of formulation types, including: solution, suspensions, as well as technical lyophilization, which removes the water content, which allows increasing the shelf life and stability of some vaccines (Single use Support Pioneering). Among the components (Public Health Institute (ISP), n.d.) that accompany the antigen, which help maintain the vaccine's efficacy during storage, there is, for example, magnesium chloride, lactose and sorbitol; in addition, they contain adjuvants, such as aluminum salts, whose function is to promote the manufacture of antibodies against the vaccine, in such a way that they can increase the immune response against the vaccine antigens. Also, in some vaccines antibiotics are used in small quantities in the manufacturing process, as a preventive measure against contamination of the cells of the culture where the antigen originated. Likewise, preservatives are used to eliminate possible bacterial or fungal growths, which could affect the quality of the vaccine, which are mainly used in vaccines to be marketed in multidose vials.

Quality control

What is quality control in the Biomanufacturing of vaccines, biological and biotechnological products, and what does it consist of?

Quality control is essential to ensure the results issued by a laboratory in relation to the samples being analyzed. This process is systematic and ensures that each stage of the analysis is reviewed and adjusted, as necessary, to meet specific standards. Without effective quality control, the precision and accuracy of results can be compromised, which could lead to incorrect decision making and ultimately to a loss of confidence in the laboratory results (American Society for Testing and Materials, 2022). To ensure the reliability of testing in a laboratory, it is crucial to meet certain basic requirements, this includes regular calibration of equipment, to ensure that the instruments provide accurate measurements. Method validation is equally important to confirm that the techniques used are suitable for the objectives of the proposed analyses, including also the

strategy for compliance with the validated status; additionally, internal quality controls and detailed documentation based on a quality management system must be carried out, which allows maintaining the precision and accuracy of the results obtained (International Organization for Standardization, 2021). Among the practical methods used in laboratories, chromatography and spectroscopy are common techniques used for the analysis of chemical components; in addition, quality control methods, such as the use of positive and negative controls, are essential to verify the accuracy of tests, regular cleaning and disinfection of equipment, along with strict safety protocols, which are essential to avoid contamination and ensure a safe and effective work environment (Harris, DC, 2015).

Quality control (QC) in the Biomanufacturing of vaccines and biological products is crucial to ensure the safety, efficacy and quality of the final product. This process covers multiple aspects, from personnel training to equipment maintenance and audits.

Different components of quality control in this field and their importance are explored below.

• Personnel
Must be highly trained and qualified to ensure the correct implementation of quality control procedures (World Health Organization, 2020). Adequate and thorough training of personnel is also important to ensure that all procedures are performed correctly and errors are minimized; personnel must have the ability to identify and correct potential errors in the manufacture process.

• Facilities
Prevents cross-contamination and ensures that conditions are optimal for the manufacture of vaccines and biological products. The facilities in which Biomanufacturing is carried out must comply with strict design and maintenance standards, to avoid contamination and ensure a suitable manufacture environment, proper management of the facilities is essential to guarantee the quality and safety of the final product (Alosert, H. et al., 2022).

• Equipment
The equipment used must be calibrated and maintained regularly to ensure its correct operation. This process prevents errors in manufacture and ensures the accuracy of the results.

• Materials
Materials must meet strict specifications to ensure the quality of the final product. The use of high purity materials is essential to avoid contamination and ensure the efficacy of the biological product. Materials used in Biomanufacturing must meet established criteria to ensure the integrity and efficacy of the final product, as proper management of materials is vital to prevent contamination and maintain the quality of the process.

• Sampling
This process must be representative and carried out following standardized procedures to ensure the accuracy of the results. Adequate sampling is essential to obtain representative and reliable results during quality control. Sampling must be carried out in a way that guarantees representativeness of the batch under study, this is crucial so that the values obtained and the accuracy of the test results are attributable solely to the product.

• Audits
Audits should be conducted regularly to assess compliance with quality standards and good practices, which allows areas for improvement to be identified and ensures that all processes comply with current regulations. Regular reviews are essential to assess compliance with quality standards and good practices, these assessments help to identify deficiencies and ensure continuous improvement in the manufacture process.

• Computers
Computer systems must be validated and maintained to ensure data integrity and process operation. Proper management of computer systems ensures that data is accurate and manufacture processes are carried out efficiently (Alosert, H. et al., 2022). Computer systems used in Biomanufacturing must be validated and maintained to ensure data integrity and proper process operation. Proper management of these systems is essential to maintain quality and efficiency in manufacture.

In the Biomanufacturing of vaccines and biological products, quality control is crucial to ensure that products meet standards of purity, efficacy and safety.

Improving manufacture processes and implementing effective batch approval specification verification practices can significantly contribute to process improvement.

These practices include ensuring that materials and finished products meet required purity requirements, identifying and resolving problems before they become major issues, and reducing the risk of product recalls and customer complaints.

Therefore, improvement of biotechnology products is achieved through adherence to good quality control practices, implementation of good practices in personnel training, maintenance of facilities and equipment, materials management, sampling, audits, and management of computer systems contributes to the accuracy and reliability of results and to continuous improvement of the manufacture process.

Some of the specific quality control methods in the Biomanufacturing of vaccines and biological products, such as impurity testing, chemical analysis and characterization testing, are:

• **Testing for impurities and related substances:** Testing for impurities and related substances is critical to ensure the product purity, methods include identification testing by FTIR spectroscopy and chemical analysis, as well as limit testing for heavy metals.

• **Heavy metal limit testing:** Heavy metal limit testing can be performed using traditional chemical methods or advanced techniques such as ICP (Inductively Coupled Plasma Spectrometry) or ICP-MS (Inductively Coupled Plasma Mass Spectrometry).

• **Optical microscopy:** Optical microscopy is a classical technique for assessing particle size distribution by direct observation of particles under a microscope (Malvern Instruments, 2022).

• **Laser diffraction:** Laser diffraction is a modern technique for measuring particle size distribution, providing accurate and reproducible data on the dimension of particles in a sample.

• **Differential Scanning Calorimetry (DSC):** DSC is used to evaluate the thermal properties of products, providing information on melting point and crystallinity, this analysis is crucial to characterize the stability and purity of the product (Rigaku, 2021).

• **Nuclear Magnetic Resonance (NMR):** NMR provides information on the molecular structure and chemical composition of products, helping to characterize and verify purity (Schering, 2022).

In summary, quality control in the Biomanufacturing of vaccines and biotechnology products not only ensures the safety and efficacy of the final products, but also reinforces reliance in the manufacture processes. Rigorous implementation of quality practices in key areas such as personnel, facilities, equipment, and audit systems ensure that each batch of product meets the highest standards. Through constant validation and improvement of these procedures, pharmaceutical companies can not only maintain quality, but also optimize the efficiency of their operations, minimizing risks and maximizing reliance on the products they manufacture.

Design of facilities for a plant for manufacturing biological medicines for human use

As stated in Annex 2 WHO good manufacturing practices for biological products Replacement of WHO Technical Annex 1 Report Series, No. 822, The World Health Organization (WHO) good manufacturing practices for sterile pharmaceutical products define and establish the required class/grade for cleanrooms to perform the manufacturing of sterile materials, according to the operations performed, including final aseptic filling. Additionally, to address the specific manufacturing processes involved in the manufacture of biological products, and in particular vaccines, the WHO guidance document Environmental monitoring of cleanrooms in vaccine manufacturing facilities: Points to be considered by human vaccine manufacturers in developing environmental classification requirements for biological product manufacturing processes (World Health Organization, 2010) can be used. Health Organization [WHO], n.d.).

According to the Spanish Agency for Medicines and Medical Devices (AEMPS), in Annex 2 of its Guide for the Manufacturing of Biological Active Substances and Biological Medicines for Human Use, it is indicated that unlike

conventional medicines (pharmaceutical products for everyday use), which are manufactured using chemical and physical techniques capable of a high degree of consistency, the manufacture of biological medicines involves processes and materials such as cell culture or extraction of living organisms, which due to their inherent variability means, in turn, that the nature and properties of the by-products obtained may vary . In line with the above, the design of vaccine manufacturing facilities will also change depending on the type of vaccine to be produced (Spanish Agency for Medicines and Medical Devices [AEMPS], 2018).

cGMP vaccine facility can manufacture (Isobox Systems sl, 2021)

- Inactivated vaccines
- Live attenuated vaccines
- Messenger RNA (mRNA) vaccines
- Subunit, recombinant, polysaccharide, virus-like particle (VLP) and conjugate vaccines
- Toxoid vaccines
- Viral vector vaccines
- DNA vaccines

Likewise, it is necessary to adapt the degree of environmental control of particles and microbial contamination of the manufacturing premises according to the active substance, intermediate products or the final product, the manufacturing stage, the potential level of contamination of the starting materials and the risks associated with the product. The environmental monitoring program must be complemented with the inclusion of methods for the detection of specific microorganisms (molds, yeasts, anaerobes, etc.) when indicated by the quality risk analysis process. Consequently, manufacturing and storage facilities, processes and environmental specification of the areas must be designed to prevent external contamination of the products, since this is more appropriate than the detection and elimination of the same; although it is likely that contamination becomes evident during processes such as fermentation and cell cultures (AEMPS, 2018).

The design must also comply with strict Good Manufacturing Practices regulations and other international reference regulations, which guarantee the quality and safety of these products that usually contain therapeutic proteins, immunogens and other biologicals, ensuring the appropriate conditions for their manufacture, handling and storage. To do this, it is necessary to take into account some elements such as:

- Type of vaccines to be produced
- Biosafety levels (BSL), according to the agents of interest or vectors used
- ISO classifications/GMP requirements suitable for clean area of vaccines
- Process phase (R&D, preclinical and clinical phases, large-scale manufacturing)
- Dimensions, equipment inside the room, number of people involved in the process
- Vaccine manufacture capacity/number of doses expected to be produced, among others

Key aspects in the design of such facilities, as indicated in Annex 2. Manufacturing of biological active substances and biological medicines for human use (AEMPS, 2018) and Annex 2, WHO, good manufacturing practices for biological products replacement of Annex 1 of WHO, Technical Report Series, No. 822., (WHO (sf)):

- "Dedicated manufacture areas should be used for handling live cells capable of persisting in the manufacturing environment. Dedicated manufacture areas should be used for the manufacture of pathogenic organisms (i.e., Biosafety Level 3 or 4)."

- "Air handling units should be designed, constructed and maintained to minimize the risk of cross contamination between different manufacture areas and may need to be area specific. Consideration should be given to the use of single-pass air systems based on Quality Risk Management principles."

- "Positive pressure areas should be used for the processing of sterile products, but the use of specific negative pressure areas at the point of exposure to pathogens may be acceptable for containment reasons. Where negative pressure areas, or safety cabinets, are used for the aseptic processing of materials with a specific risk (e.g. pathogens), these areas should be surrounded by a positive pressure clean zone of an appropriate grade. These pressure cascades should be clearly defined and continuously monitored by appropriate alarm systems."

- "Primary containment must be designed and periodically reviewed to ensure prevention of the escape of biological agents into the immediate work environment."

• "Drainage systems must be designed so that effluents can be effectively neutralized or decontaminated to minimize the risk of cross-contamination."

• "Equipment used in the handling of cells and living organisms, including that used for sampling, must be designed to avoid any contamination during the process."

• "Primary containment equipment should be initially designed and qualified to ensure its integrity, to ensure that escape of biological agents and/or materials into the immediate work area and outside environment is prevented. Periodic testing should then be performed in accordance with relevant guidelines and safety risk management principles to ensure that the equipment is in proper working order."
• "Where extraction air filtration is required, safe filter replacement should be ensured or bag-in-bag housings should be used. Once removed, filters should be appropriately decontaminated and destroyed. In addition to HEPA filtration, other inactivation technologies such as heat inactivation and steam scrubbing for extraction air may be considered to ensure effective inactivation of pathogens in biosafety risk groups 3 and/or 4" (WHO (sf))

• "Whenever possible, "cleaning in place" and "steam in place" ("sterilization in place") systems should be used. Valves on fermentation tanks must be fully steam sterilizable" (AEMPS, 2018).

• "Due to the variability of biological products or manufacturing processes, relevant/critical raw materials (such as culture media or buffers) have to be measured or weighed during the manufacture process."

The manufacture of vaccines at a local level is an opportunity for growth for the country, both in the educational field, by incorporating new careers, and in the labor field, since it is an opportunity for national development that can bring a lot of knowledge and sources of employment. In the area of public health, it also has a positive impact, since vaccines are the best tool to prevent diseases and reduce the use of antibiotics; and at the regional level, by achieving pharmaceutical independence, it will allow us equitable access for the entire population at the right time.

Conclusion

The manufacturing of vaccines through any platform represents a complex process, which requires a technological and pharmacotechnical combination and which, in addition, is supervised by regulatory agencies, and must adhere to strict compliance with Good Manufacturing Practices (GMP) regulations, since vaccines are an important tool for public health systems in the treatment and prevention of existing and emerging diseases, which is why it is important that they are safe, effective and of quality, and that equal access to vaccines is also guaranteed for the entire population. Considering the emergence of new diseases in recent years, such as the COVID-19 pandemic, it becomes an imperative need to invest in pharmaceutical independence and strengthen research and development of vaccine manufacture, as well as manufacturing infrastructure, which will allow for better management of future diseases and protect public health more effectively worldwide.

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