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Review Article

A Review of the Establishment of the Seed Lot System in the Production of Biological Products and Its Importance

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Abstract

Today, due to the importance of diseases controlled by vaccination, the production of biological products is of great importance in ensuring public health, so producing high-quality biological products plays an important role in maintaining public health. One of the most important principles of manufacturing high-quality and efficient biological products is using suitable seeds based on standard principles. To produce a suitable seed for continuous use for mass production of biological products, the seed must be defined according to certain principles and foundations. These principles are formed in the form of a seed lot system. In this review article, all the requirements for the establishment of a seed to produce a biological product include general seed information, including basic and seed information and microorganisms, seed-specific information including seed passage levels, propagation method, seed storage conditions, coding and labeling, identification information and design of suitable laboratories for passage, seed propagation, and storage, determination of seed characteristics including all necessary tests to determine seed identity, purity, potency, efficacy, stability, safety and also all the necessary information for documenting and storing seeds has been studied. Also, this study discusses the method of preparing all the necessary information for establishing a seed lot system, especially determining the characteristics of seeds. Based on the study's results, a complete and comprehensive seed lot system has been formed that can be used to prepare, propagate, passage, and store seeds used in the production of biological products.

Keywords: Vaccine, Seed, Lot, System, Characterization

1. Context

The starting point for producing all microbial vaccines is isolating the appropriate infectious agent. Such isolates have usually been derived from human infections and, in some cases, have yielded strains suitable for vaccine production very readily; in other instances, a great deal of manipulation and selection in the laboratory have been needed before a suitable strain has been obtained. For example, bacterial strains may need to be selected for high toxin yield or production of abundant capsular polysaccharides; viral strains may need to be selected for stable attenuation or good growth in cell cultures.

Once a suitable strain is available, the practice is to grow, often from a single viable unit, a substantial volume of culture, which is distributed in small amounts in a large number of ampoules and then stored at −70°C or below or freeze-dried. This is the original seed lot. From this seed lot, one or more ampoules are used to generate the working seed from which a limited number of vaccine batches are generated. A seed lot system is a system in which successive batches of a

product are derived from the same master seed lot at a given passage level to prevent the unwanted drift of properties that might ensure from repeated subcultures or multiple generations (1, 2).

For routine production, a working seed lot is prepared from the master seed lot. The final product is derived from the working seed lot and has not undergone more passages from the master seed lot than the vaccine shown in clinical studies to be satisfactory with respect to safety and efficacy. The origin and passage history of the master seed lot and the working seed lot is recorded (3).

The seed lot system ensures that the working seed produced for the daily production of the biological products from the master seed is produced in a minimum passage and with a certain number of passages, so the product is uniform and free of possible deviations (3, 4).

2. Evidence Acquisition

Due to the high importance of the seed lot system in producing biological products, this article reviews how to establish this system. The purpose of this article is to review all the aspects required to establish a seed lot system. This article describes how to collect information from vaccine seeds, analyze the collected information, apply the analyzed information, the necessary tests, and how to perform these tests to determine the characteristics of the seeds.

Extensive searches have obtained part of the content of this article in published articles in this field, but most of these are the result of the author's summaries and experiences in this field.

The seed lot system establishment determines and examines the two seed specifications. The first is the general characteristics, and the second is the specific and functional characteristics of the seed.

2.1. Seed General Information

In general information, all of the general seed information is determined. This result specified, introduced, and identified the seeds. The result of general seed information help vaccine manufacturers to have accurate basic information about the seeds used in the production of a biological product. This information also identifies the type of culture medium, serum, trypsin, type of laboratory animal, and antibiotics required for seed growth and propagation in order for the seed to be in optimal growth conditions. Using this information, vaccine manufacturers avoid potential error testing and select and plan the most effective and best process for seed growth and propagation to produce the product. The first step in this section is the seed specifications, which are very important for planning the annual mass production of organic producers. In other words, the information leads to proper and effective planning for producing products in bulk and in planned volume.

The seed leveling also determines the level of seed passage, which is very important in the production of biological products because accurate identification of these steps does proper planning regarding seed storage volume for different years of production. In addition, this information allows the manufacturer to select only one suitable working seed for use in production and has a suitable reserve based on the amount of production.

The seed propagation shows that the seed has been cultured and sub-cultured several times. Also, the information obtained from this section determines how to culture the seeds and the suitable substrate for seed culture.

The seed storage conditions show under what conditions the seed should be stored and how it should be stored. The resulting information provides proper storage and maintenance of the seed, which is very important for the maintenance of this valuable storage of manufacturers.

Seed coding and labeling identify all seed information at a glance to minimize possible errors in the production process. Especially in the biobank, the seeds are stored at different levels of passage and different working levels. This is also especially important for manufacturers who produce multiple products.

The proper design of seed production laboratories creates a unique system for handling seeds in centers

where various biological products are produced. The design of laboratories based on the seed lot system allows the seeds to be manipulated in separate places. Also, the design of laboratories based on the seed lot system provides specific conditions for different tests of a seed a different levels.

2.2. Seed Characterization

The Identity test shows that the studied seed is precisely the desired seed and does not create any ambiguity in the production process regarding the identity of the seed used. This is critical to the production of a particular product and addresses manufacturers' concerns about the definitive production of a product**.** Proof of this in various aspects of physicochemical, serological, molecular, sequencing, etc., creates a reliable process in the production of the product and maximizes the manufacturer's confidence in the product. Especially in sequencing, which is done in different ways, this assurance is created for the producer with a high percentage (5, 6).

In determining the phenotypic characteristics, the results show that the studied seed has passed all the phenotypic characteristics, such as tissue tropism, virulence reduction, and neurovirulence characteristics, and is approved in this regard. The purity tests show that the seed has no bacterial, fungal, or mycoplasma contamination (different mycoplasma species) and is entirely pure. Also, the results of the experiments of this group in the category of adventitious agents indicate that the studied seeds are not infected with adventitious agents, especially viruses, and the desired seeds contain only the relevant microorganisms (7).

The other tests, such as virus titers or microbial counts, show how potent the seed is and whether the product has enough ability to control the disease.

Seed stability studies also determine the selected seed stability condition during storage and how long it can be used to produce the product. Instability studies, in addition to temporal stability, genetic stability is also examined, which determines the possible changes of the seed or its return to virulence during storage.

The seed safety test also determines whether the seed is appropriately suitable. The result of this test in the seed and seed lot system creates sufficient confidence for the manufacturers of the safety of the manipulated seeds.

2.3. Seed Documentation and Storage

After determining all the general information and the specific characteristics of the seed, if the studied seed has passed all the necessary criteria, it can be stored in the specified conditions. Specified storage conditions seeds determine what specific storage conditions each seed needs, and specify where each seed is stored in centers where several products are produced and, of course, several seeds are tested and stored, and what arrangements have been made for the separation of the seeds.

3. Results

For the establishment of a seed lot system in the production of biological products and preparation of seed certificate, the following steps (10 steps) are performed in order:

3.1. Seed General Information Record

For this step ,the following topics should be answered, and the data was collected:

Seed initial code, source (a record of the origin), date of isolation, strain, species, and seed genus, the name of the final product made from this seed, and received date must be registered. The animal model used for this seed must be specified. This section should also specify the primary cell and secondary cell cultures (master cell bank and working cell bank) and the cell lines used for seed propagation and storage. The approval of seeds by reputable health centers of the country of origin or international authorities is also required. The origin of serum and trypsin used in cell culture, the result of tests performed on them, and the serum and trypsin health certificate for the BSE factor must be specified.

The type of media, the characteristics of the culture medium, the complete composition of the culture medium, and the analysis sheet of the materials used in

it should be specified with a valid reference and the result of the tests performed on the culture medium.

If the vaccine comprises different components, information about each component must be provided in its entirety and separately (active ingredient and excipients) (8, 9).

3.2. Seed Specification

In this section, the information related to the passage history of the desired seed along with the relevant seed information (includes the number of vials, volume of each vial, batch number, passage date and passage number, and including purification and characterization procedures) for different stages of seed (with the following definitions) is collected and recorded in the relevant tables (10, 11).

3.3. Seed Leveling

In the seed lot system, vaccine seeds are classified to establish the surface and increase the number of seeds without losing the required seed characteristics as follows:

- Received Seed: means the seed that has been received from a specific source and has entered the production center.

- Parent Seed: The seed imported from the original seed (received seed) has been prepared during a certain passage.

- Master Seed: A culture of a microorganism distributed from a single bulk into containers in a single operation in such a manner as to ensure uniformity, prevent contamination, and ensure stability. A master seed lot in liquid form is usually stored at or below -70°C. A freeze-dried master seed lot is stored at a temperature that ensures stability. The master seed is obtained from the parent seed during a certain passage.

- Working Seed: A culture of a microorganism derived from the master seed lot with a specific passage intended for use in one or more production batches and ready to make the relevant vaccine. Working seed lots are distributed into containers and stored as described above for master seed lots.

Vaccine production is not normally undertaken using more than 5 passages from the master seed lot (12, 13).

3.4. Seed Propagation

Specifying the minimum and a maximum number of subcultures of each parent and master seed lot before the production stage. The methods used for the preparation of seed cultures, preparation of suspensions for seeding, techniques for inoculation of seeds, titer and concentration of inocula, and the media used, are documented. It shall be demonstrated that the characteristics of the seed material (for example, dissociation or antigenicity) are not changed by these subcultures (14). The conditions under which each seed lot is stored are documented. For viral seeds, the master seed lot and all subsequent passages are propagated on cells, on embryonated eggs, or in animals that have been shown to be suitable for vaccine production, and where applicable, using substances of animal origin that meet the requirements (15, 16).

3.5. Seed Storage Condition

The information about the conditions and location of seeds in each of the 4 steps was recorded in the relevant tables. This information includes the original backup freezer code, storage temperature, stabilizer, and storage form.

3.6. Seed Coding

Each of the vaccine seeds in each stage should be explicitly coded according to specific rules for identification purposes, so that the following should be included in the coding: the name of the microorganism (specifying the genus, species, and strain briefly), the seed passage stage with the first letter of the passage stages specify (R, P, M, and W respectively for Receive, Parent, Master, and Working), and the number of passages numerically.

3.7. Seed Labeling

Each seed vial must be labeled according to specified rules. This label must include the following: the logo of the product manufacturer, seed code, seed source, year of seed preparation, and batch number of seed preparation. Also, to avoid possible mistakes in mixing the seeds, special coloring should be considered for the text, and the margin of the label, which firstly determines what stage of the seed is in the passage, and

secondly determines what kind of microorganism the seed is (especially in a center where both viral vaccines and bacterial and parasitic vaccines are produced).

3.8. Laboratory Designing

The following laboratories should be designed and deployed to perform seed characterization tests (6):

3.8.1. Cell Bank Laboratory

In this laboratory, while collecting the necessary information for the cells, in order to prepare the necessary documents, the cells required for the characterization tests of viral seeds (cell-based seeds) are obtained from reliable sources. Then the cells are passaged, and the mother and working cells are prepared. Then they are stored in nitrogen tanks. When needed to grow and multiply the relevant viruses, the cell is removed from the nitrogen tank, and after preparing the cell under appropriate logarithmic growth conditions, the cell is sent to a virus laboratory to be used for the growth and propagation of the virus.

3.8.2. Virus Bank Laboratory

The virus laboratory in the seed and cell lot system includes the following two laboratories:

3.8.2.1. Cell-Based Virus Laboratory

All cell-based viruses are examined and studied in this laboratory. This laboratory performs all the tests needed to determine the characteristics of cell-based viral seeds. In this laboratory, the cells sent from the cell culture laboratory are used for all viral seed characterization tests.

3.8.2.2. Egg-Based Virus Laboratory

All egg-based viruses are examined and studied in this laboratory. This laboratory performs all the tests needed to characterize egg-based viral seeds. Embryonic eggs (SPF eggs or clean eggs, depending on the test) are prepared on different days of embryonic development depending on the virus and are used for characterization tests in this laboratory.

3.8.3. Bacterial Bank Laboratory

In this laboratory, bacterial seeds are examined. This laboratory studied all the tests needed to determine the characteristics of the bacterial seeds that the bacterium itself should be tested on.

3.8.4. Serology Laboratory

All serological tests used to determine the characteristics of viral and bacterial seeds, such as ELISA, HI, SDS-PAGE, Western blot, etc., are performed in this laboratory.

3.8.5. Molecular Laboratory

In this laboratory, all the molecular tests required to determine the properties of bacterial and viral seeds are performed. Tests such as PCR, RTPCR, sequencing, etc., are performed in this laboratory.

3.9. Seed Characterization Tests

The tests required to determine the characteristics of seeds for the main stages of seed (master seed and working seed) are divided into 8 main groups based on the following pattern, in which the relevant tests should be performed. In the tests on the master seed lot described below, the organisms used are generally not more than 5 passages from the master seed lot at the start of the tests, unless otherwise indicated. Where the master seed lot is contained within a permanently infected master cell seed, the following tests are carried out on an appropriate volume of virus from the disrupted master cell seed. Where relevant tests have been carried out on disrupted cells to validate the suitability of the master cell seed, these tests need not be repeated (14, 17-19).

3.9.1. Identity Test

A suitable method shall be provided to identify the vaccine strain and to distinguish it as far as possible from related strains. In this group, two categories of experiments should be performed as follows (2, 15):

3.9.1.1. Bio Physico-Chemical Tests

In this test, three series of tests must be performed:

1- Metabolic Characterization: For metabolic characterization, the following tests should be performed:

Metabolic pattern, Specific enzyme tests, Identification Kits, Oxidative/ fermentative, Utilization

of sugars, Utilization of substrate, and Catalase tests.

2- Morphological and staining characterization: For morphological and staining characterization, the following tests should be performed:

Shape, Arrangement, Irregular form, Motility, Gram reaction, Size, Culture characteristics, Colonies, Turbidity and Growth in broth, Moisture content, and pH tests.

3- Physiological characterization: For physiological characterization, the following tests should be performed:

Aerobic growth, Anaerobic growth, Phage susceptibility, Temperature range, optimum temperature, pH range, Nutrition, Growth factors, Growth in selective media, and Heat resistance tests (20, 21).

3.9.1.2. Serological Tests

In this category, perform the types of serological/immunological tests required to identify the desired seed as follows:

1- ELISA: After injecting the evaluated seeds into the target laboratory animal or chick, blood sampling and serum isolation are performed, and the usual ELISA methods should examine the desired sera.

2- V.N. (Specific antiserum): Evaluation of specified antigen with specific antiserum and determination of neutralization index (Neutralization index = N.I.) by serum neutralization method (alpha method) in embryonic SPF eggs or cell cultures.

In addition, Western blot and Fluorescent antibody tests are used in some cases to identify the seeds (22, 23).

3.9.1.3. Molecular Tests

Based on the specific gene of the desired seed and the design of specific primers, PCR or R.T.- PCR tests are used to confirm the desired gene. The other tests for molecular identification are Mol % G+C, DNA hybridization, and RFLP (24-27).

3.9.1.4. Sequencing

To determine the identity of the seed by sequencing method, all or part of the seed genes are sequenced, which in the first type is called complete sequencing (full-length sequence or) and in the second type is called partial sequencing (gen or toxin). In addition, a new generation of sequencing NGS is being used to identify seeds (28-30).

3.9.1.5. Other Identity Tests

In each seed, in addition to the identification tests mentioned, tests should also be performed as complementary tests in this section, such as for infectious bursal disease vaccine seeds, tests such as stock Bursa-Body Index test, and immune suppression test are performed to verify seed identity.

3.9.2. Phenotypic Characterization of Seed

The following methods are used to determine the phenotypic characterization of studied seeds (7, 31):

3.9.2.1. Assessment of Tissue Tropism

To determine the tissue tropism of the vaccinal studied seed, it must be determined which tissues the seed reproduces and is effective. For this purpose, the following method is used:

A certain number of target hosts of a certain age and by a specified method were vaccinated with the desired strain. Virus isolation and the reverse transcription–polymerase chain reaction technique were employed to detect the virus in various tissues and body fluids for specified days following vaccination. Thus, based on the amount of bund taken from different tissues, the tissue tropism of the desired seed is determined.

3.9.2.2. Attenuation Properties

To determine the changes in the desired seed attenuation properties, a certain number of passages are sown in the appropriate laboratory host. After the passages are performed, the virulence of the studied seed is measured in the target host. There should be no change in seed virulence in the target animal, such as host mortality. Also, after determining the seed sequence after the passage, there should be no specific change in the seed sequence (16).

3.9.2.3. Assessment of Neurovirulence

Master virus seeds derived from wild-type viruses known or suspected to possess neurotropic or neurovirulent properties.

3.9.3. Purity and Sterility Tests

Various purity tests are required in this group to ensure seed purity. If the master seed lot contains living organisms other than the species and strain stated, it is unsuitable for vaccine production. The tests required in this group are as follows (32, 33):

3.9.3.1. Bacterial Agents Detection Test

Sterility testing should be performed for any bacterial contamination. Use Blood agar, Brain Heart Infusion (BHI) agar, and Tryptic Soy Broth (TSB) to identify aerobic bacteria. Also, be cultured to identify anaerobic bacteria in Thioglycollate broth. To detect various bacteria, agars, and broth cultures, media must be incubated at 37 ° C and 25 ° C, as well as aerobic and anaerobic conditions with carbon dioxide. The master seed lot complies with the test for sterility.

3.9.3.2. Fungal Agents Test

The presence of any fungal contamination in the seed should be investigated using Sabouraud Dextrose Agar (SDA).

3.9.3.3. Mycoplasma or Spiroplasma Test

To evaluate mycoplasma species contamination, the seed was cultured on a specific culture medium of broth and agar (Pleuropneumonia-Like Organisms (PPLO)) and incubated for 37 weeks at 37 ° C. The master seed lot complies with the test for mycoplasmas (culture method and indicator cell culture method).

3.9.3.4. Extraneous Agent Tests

The requirements for freedom from extraneous agents are stated below (34-36):

Preparations of monoclonal or polyclonal antibodies containing high levels of neutralizing antibody to the master seed are made on a batch basis, using antigen that is not derived from any passage level of the virus isolate, giving rise to the master seed. Each batch of serum is shown to be free of antibodies to potential contaminants of the seed and is shown to be free of any non-specific inhibiting effects on the ability of the seed to infect and propagate within cells (or eggs, where applicable).

Other methods are used to remove or neutralize the seed virus if such a serum cannot be obtained.

If the seed lot would interfere with the conduct and sensitivity of a test for extraneous viruses, a sample of the master seed lot is treated with a minimum amount of the monoclonal or polyclonal antibody so that the vaccine seed is neutralized as far as possible or removed. For mammalian vaccines, the seed lot or the mixture of seed lot and antiserum is tested for freedom from extraneous agents as follows:

The mixture is inoculated onto cultures of at least 70 cm2 of the required cell types. The cultures may be inoculated at any suitable growth stage up to 70% confluency. At least one monolayer of each type must be retained as a control. The cultures must be monitored daily for a week. At the end of this period, the cultures are freeze-thawed 3 times, centrifuged to remove cell debris, and re-inoculated onto the same cell type as above. This is repeated twice. The final passage must produce sufficient cells in appropriate vessels to carry out the tests below. Cytopathic and haemadsorbing agents are tested, and techniques such as immunofluorescence are used to detect specific contaminants for the tests in cell cultures.

In extraneous agent detection tests, seeds should be evaluated for the following agents: Cytopathic viruses, heamadsorbing viruses, bovine and porcine viruses, poultry viruses such as lymphoid leucosis, infectious bronchitis, chicken anemia syndrome, encephalomyelitis, turkey rhinotracheitis, reoviruses, salmonella pullorum, mycoplasma galisepticum, Mycoplasma syniviae, retroviruses and test for specific viruses, such as BVDV, BLV.

In vitro and in vivo methods are used to detection of these agents. In in vitro methods, the primary and diploid cell cultures and cell lines were used. The master seed lot is inoculated onto primary cells of the virus's origin species, cells sensitive to viruses pathogenic to the species for which the vaccine is intended, and cells sensitive to pestiviruses.

Cytopathic effects and heamadsorbtion, H.I., rapid agglutination, antibody production assay, and specific kit for antigen detection are evaluated in this method. In vivo methods, lab animals such as mice, Guinea pigs, etc., are used. If the master seed lot contains living organisms other than the virus of the species and strain stated, or foreign viral antigens, it is unsuitable for vaccine production (37, 38).

3.9.4. Titration/ Colony Count

In this section, the desired seed titer is determined using a number of tests. These tests include CCID50 and EID50 for the viral seeds and colony count and viable colony count for bacterial seeds (18).

3.9.5. Efficacy/ Potency

To determine the potency/ efficacy of the studied seed, the product is inoculated to the target host by a specified dose, and after a certain period of time, the desired seed strain is challenged. After the challenge, the study groups are evaluated daily. Any reactions are recorded in the study groups. Based on this, the ability of the studied seed is determined (39).

3.9.6. Stability Study

In this group of experiments, the stability of the desired seed during the storage period in the relevant shape by determining the seed titer at the beginning and the specified intervals of seed storage until the end of the expiration date should be evaluated (32, 33).

3.9.7. Reversion to Virulence or Genetic Stability

For seed analysis in reverse to virulence in the case of attenuated vaccinal seeds, depending on the type, the seed is inoculated with a specific dose to the target host. After a few days, the target tissue of the seed is removed, and after preparation, it is inoculated to the target hosts. This operation must be repeated 5 times. Finally, possible histopathological lesions on the target tissue are examined based on whether they reverse virulence or not for the desired seed. Also, after a few passages, the desired seed is sequenced. There should be no difference in the sequence determined after the passage with the initial seed sequence (40-42).

3.9.8. Safety

Depending on the type of seed, five to ten doses of the seed are injected into a sensitive laboratory host. Injected hosts are evaluated daily for 14 to 21 days. The absence of any local reaction, general reactions, weight loss, and mortality indicate that the studied seed is safe. Otherwise, the safety of the desired seed is not approved.

Based on the sum of the results obtained from the above-mentioned studies and tests, it is determined whether the desired seed can be used in the studied stage (working or master) to produce a biological product or not. Each case study in the seed lot system must be discussed and analyzed (19).

3.10. System Suitability

Based on the results obtained and compared to standard control seeds, if the relevant specifications are passed in the case of master seeds in all the tests performed, this seed is ready for passage and entering the working seed stage. Otherwise, if the specified specifications are not implemented in any of the above tests, the seed will not be usable and must be omitted. In the case of working seeds, the seeds can be used to produce the desired biological product if the tests performed compared with the standard controls have passed the relevant specifications. Otherwise, the seed will be removed from the vaccine production cycle.

3.11. Preparation of Documents

To establish a seed lot system, the necessary documents for this system must be compiled and controlled. These documents include (42):

3.11.1. SOP

Standard test and procedure instructions should be developed separately. Seed re-testing policy SOP should also be included in these documents.

3.11.2. Test Record

The test record should be completed for recording each experiment's results.

3.11.3. Seed Certificate

All information obtained from seed studies reviewed in this article, including microorganism information,

seed passage information, seed storage information, seed coding, and labeling information, and seed quantity information, as well as the results of all seed characterization tests, should be included in the seed certificate.

3.12. Seed Storage

One of the seed lot system's essential foundations is the seeds' maintenance and storage. Seeds should be stored in suitable conditions in -86 ° C freezers; these freezers should have the highest level of reliability. Freezers must be connected to a stabilizer and uninterruptible power supply. After placing the seeds in the relevant freezers, the temperature and humidity of the freezer room should be checked daily and twice a day (morning and afternoon) and recorded in special forms. The seed room temperature should be 20 to 25 degrees to minimize pressure on the freezers. The freezer temperature, set in the range between -75 ° C to -85 ° C, must be monitored by the data logger for 24 hours. If there is a problem in any of the freezers that require time to repair or troubleshoot, immediately remove the contents of the defective freezer and put it in full in the backup freezer, which is provided for this purpose in the freezer room.

During seed storage, the seed should be continuously monitored for the following:

Seed expiration date, date of periodic testing or tests to determine the characteristics of the seed, any event that occurred during the storage period of the seed, such as possible defects in the freezer of the seed storage room, such as an increase in temperature or possible failure of the freezer or any similar incident species and any accident caused to the seeds during storage such as broken vials or similar incidents.

The sum of the studies and the analysis performed will lead to the compilation of a set of documents, which will be a schematic and principled roadmap for manufacturers to produce biological products in the seed lot system.

Finally, the results of all the above studies and tests will form a certificate for the studied seed, which describes all the general and specific characteristics of this seed in detail. At all stages of passage, use, propagation, and storage of this certificate's seeds should be considered a roadmap (37, 43).

4. Conclusions

Growing practical and legal requirements in all fields of medicine and biology require new techniques and the creation of supply chains that represent comprehensive quality assurance and the appropriate method for identifying and recording individual activities at each stage and at all stages of production. Therefore, the application of such a control process called Seed Lot System in the first production stage of biological products, i.e., seed preparation, can be done only by creating a good system, and non-compliance with the principles is considered non-compliance with GMP principles (44).

Establishing this system of preparation and maintenance of strains (seed lot system) will ensure the manufacturers that always a sufficient seed population with the desired quality and health will be available. Maintaining such valuable banks in a secure and controlled environment is also very important. A biologically reliable system in this field not only allows the manufacturer to perform quality control tests considered in the management of the Seed Lot System of each product based on reference standards (usually identification, sterility, purity, harmlessness, and capability) but also provides safe short-term and long-term seed storage (45).

In addition, establishing the Seed lot System is essential for clinical studies and producing and supplying products to the consumer market (46).

Unexpected events working with strains along with microbial and viral contamination are always a serious risk to the individual and the strains being cultivated and can yield valuable strains that are purchased at exorbitant costs or the result of months and years of continuous work and effort, destroy and then contaminate the product or product or disrupt research

and diagnostic results. On the other hand, repeated passages and long-term use of strains eventually cause changes in their hereditary or natural characteristics, ultimately reducing their functional value or making these strains unusable (47).

In the seed lot system, all the vaccinal seeds used are coded and labeled and have a certificate, and their reproduction and storage are according to the defined principles and characteristics. Establishing such a highly secure system will be one of the critical issues for the successful production of biological products. To prevent the emergence of unwanted traits following culture or passage of microorganisms, the production of biological products by microbial, cell culture or culture or propagation in embryonic eggs or animals should be done using standard seeds and on the base of the seed lot system. Based on the principles of the seed lot system.

The number of passages between the seed series and the final product must be in accordance with the product manufacturing license, and this fundamental relationship should not change in increasing production. Seed series characteristics should be adequately determined and tested for contaminants. Their suitability for use must be established by examining the conformity of the specifications and quality of a series of consecutive product structures. The vaccine seed series should be created, stored, and consumed in such a way as to minimize the possibility of contamination or alteration. Seed production should also be done under well-controlled conditions to protect vaccinated seeds and, if necessary, staff. No other living or infectious material should be handled simultaneously in the same environment or by the same individuals during seed generation (48).

In the seed system, first, complete documentation of general seed information used to identify seeds is made available to manufacturers of biological products; and second, complete information on seed characterization that the producer can use to identify if the seed decides, third will have very clear information on the storage conditions of the seed in question, fourth complete documents will be prepared from the seed under study, including a seed certificate, which will also be available to producers, and in case of need, it can be provided to the supervisory authorities on product production (49, 50).

In general, the importance of the seed lot system can be summarized as follows:

1- To have safe, pure, and effective products
2- To have valid quality control tests
3- To comply with cGMP
4- Permanent production
5- To have good biological research and development
6- To have security in production

Authors' Contribution

Study concept and design: S. S.
Acquisition of data: S. S.
Analysis and interpretation of data: S. S.
Drafting of the manuscript: S. S.
Critical revision of the manuscript for important intellectual content: S. S.
Administrative, technical, and material support: S. S.

Conflict of Interest

The authors declare that they have no conflict of interest.

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