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Research Article

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Process Validation and Critical Regulatory Requirements in Manufacturing of Inactivated Veterinary Vaccines

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Abstract

Process validation is the most critical regulatory requirement for licensed biopharmaceuticals and vaccine facilities. It is also considered as an economic issue through understanding and controlling any process and subsequently minimizing the processes failures. The process design (PD), process qualification (PQ) and continued process verification (PV) are the main three stages for industry for process validation. It was defined as the collection and evaluation of data, from the process design stage throughout production, to establishe a scientific evidence that a process is consistently delivering high quality products and in accordance with the principles of Good Manufacturing Practice (GMP). The challenges of vaccine production process are not limited to its complicated details which may change the validity of the process but also the cross process that still the biggest challenge. Therefore, process validation in biopharmaceutical industries has the high priority specially vaccine production. In conclusion, continuous monitoring and validation of inactivated veterinary vaccines has the great impact on defects, nonconformance decreasing and processes improvement. Also the critical parameters of process validation of inactivated veterinary vaccine manufacturing are highlighted.

Keywords: Process, Validation, Verification, Qualification, Biopharmaceuticals, GMP, Vaccines

Introduction

Every day the public needs for safe and effective vaccines become larger and stronger. These needs for pharmaceutical, biopharmaceutical and vaccines required a continuous development in the manufacturing process to achieve the customer needs, also the development and manufacturing of a new vaccine is a great challenge due to complexity of the technology, the need for expensive specific facilities and the severe regulatory desires [1]. Validation is an important process which proves that the facility still able to produce a high-quality product with minimum chance to fail in this objective. This process begins with good understanding of the requirements and the essential to design a process that will be accomplished of finally meeting fixed specifications without being subjected to nonconformities within a defined range of predetermined operating parameters [2].

The primary regulator of drug and biological products has defined a number of chief expressions for the pharmacological and biopharmaceutical industries. These definitions can be found on the Food and Drug Administration (FDA) web site (www.fda.gov) and in the related Code of Federal Regulations (CFRs) and regulation documents. One of the terms vital to the biotechnology industries is validation; it is defined by the FDA as: "The process of demonstrating, through documented evidence, that a process, procedure, piece of equipment, analytical method, or facility will constantly produce a product or result that meets predetermined specifications and quality attributes." [3, 4, 5]. In the present review, the critical prameters of validation process of inactivated vaccines which need continous monitoring are discussed the international requirements.

Process validation

Validation is an external check on the performance of a system and ultimately the entire manufacturing process. If the process performs properly, it should produce a product that meets predetermined specifications as shown in validation V-model in Fig. (1). If it does not perform properly, a step in the process exists that is either inadequately understood or is not performing as designed [6,7,8]. The V-model provides a logical sequence that helps to organize the complex activities. The left arm of the "V" represents the planning / specification phases such as User Requirements Specification (URS), Functional Specification (FS), Detailed Design (DD), and the right arm of the "V" represents the execution-validation phases such as Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ). Bio-manufacturing organizations must prove that the production process will consistently create a product that meets all of the specifications or quality attributes that have been established for that product [9, 10]. To accomplish this, organizations must ensure that: the premises, equipment, and

utilities all working, performing probably and QC's analytical methods are performed as expected, beside that each stage of the production process funds to a final product that meets all of the quality characteristics and specifications [11].

In vaccine manufacturing validation can be defined as the action of proving in complying with GMP, requirements that any procedure, process, equipment, material, activity or system leads to the projected results [12,13,14]. There should be wide-ranging validation of manufacturing processes to ensure the endless conformity of vaccine batches to mandatory standards (all qualification and validation activities should be planned and take the life cycle of equipment, process and product into consideration [15, 16, 17]. So that, there is a very important things to be taken in consideration during process validation as follow :

Validation activities should only be performed by well qualified personnel who track approved validation procedures [11].

A. Validation activities should only be performed by well qualified personnel who track approved validation procedures [11].
B. Validation personnel should report to a quality management or a quality assurance function, however there should be appropriate supervision over the complete validation life cycle [18].
C. The main elements of the site validation programme should be evidently clear and documented in a validation master plan (VMP) or equivalent document [19].
D. Validation also forces the bio manufacturer to observe rules about equipment, materials, procedures, and the whole production process [20].

For example, that material placed to an autoclave will be sterilized when that autoclave working appropriately. That be achievable if easy to assure that the sterilization validated using a bio indicators and acceptance shows also documents that the autoclave is working according to its design specifications and that the autoclave cycles are sufficient to sterilize the material placed within [21].

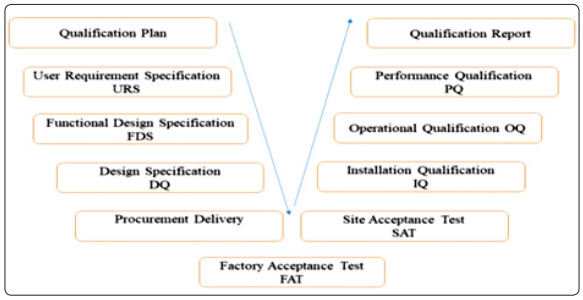

Figure 1: Validation V model – Modified after Patrick Katz

Process validation in veterinary inactivated vaccine production

The vaccine production methods (e.g., in-ovo, cell culture) and the type of vaccine (Live, killed vaccines) is well tied to each other. Vaccines can be also classified to non-adjuvanted vaccine, which has only the antigen as its main component and adjuvanted vaccine, which has two main components, the antigen (inactivated virus) and the adjuvant [22]. As vaccine technology has advanced, the methods to produce the vaccine have progressive and new vaccine chances have been manufactured. These technologies will continue to change for safer and more immunogenic vaccines [22]. Modern vaccine development is currently take advantage of a wide array of novel technologies to create safer and more efficacious vaccines including: viral vectors produced in animal cells, virus-like particles produced in yeast or insect cells, polysaccharide conjugation to carrier proteins, while DNA plasmids created in *Escherichia Coli* (*E. Coli*). From a controlling viewpoint, Quality by Design (QbD) and Process Analytical Technology (PAT) are important creativities that can be applied effectively to many types of vaccine processes. Worldwide demand for vaccines needs that a manufacturer plan to supply tens and sometimes hundreds of millions of doses per year at low cost so that he must do all the best to be sure that his process is valid to produce safe and effective vaccine [23].

Inactivated veterinary vaccine Production processes

All processes for inactivated In-ovo vaccine production are mentioned in Fig. (2). Each process of these previous processes needs to be verified and it must be within limits of acceptance criteria [24]. The limits for viable count and airborne particulate count are mentioned in Tables (1, 2) [25].

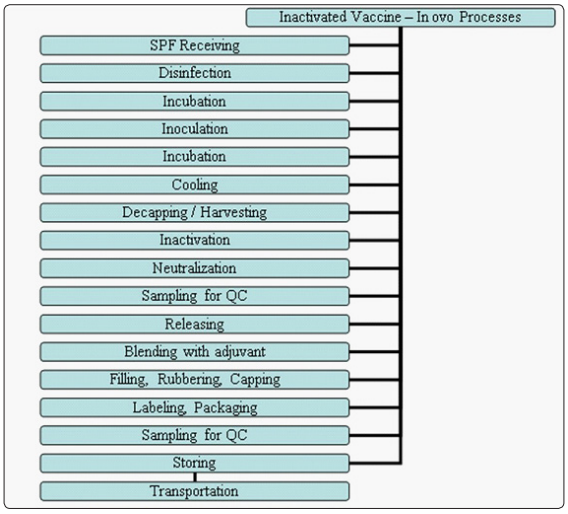

Figure 2: Inactivated vaccines -In ovo processes

Table 1: Viable count acceptance limits

Grade	At rest		In operation	
	Maximum number of particles permitted / m3		Maximum number of particles permitted /m3	
	0.5mm	5.0mm	0.5mm	5.0mm
A	3520	20	3500	0
B	3520	29	352000	2900
C	352000	2900	3520000	29000
D	3520000	29000	Not defined	Not defined

Table 2: Airborne particulate count acceptance limits

Grade	Air sample (CFU/m3)	Settle plates (diameter 55 mm) (CFU / 4 hour)	Contact plates (diameter 55mm) (CFU/ plate)	Glove print (5 fingers) (CFU/ glove)
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

It is very clear that the process validation of vaccine production and control of critical parameter is the key element to produce safe, high

quality and effective vaccine. Each process and parameter can be the root cause of a big problem if not been controlled, as example hand gloves of personnel if not been sterile the producer may be loss the full batch due to contamination [26]. Other example if the autoclave not reach to the sterilization temperature, temperature not monitored or controlled the overall tools will not completely sterile; this will due to loss batch also. Sterilization can be accomplished using live steam at a temperature of at least 120°C for not less than 30 minutes or dry heat at a temperature of at least 160°C for not less than one hour.

The limits and acceptance criteria has been mentioned in Table (1), Cleaning validation is aiming to demonstrate that the equipment is regularly cleaned of product, cleaner and infective residues to a satisfactory level, to avoid possible contamination and cross contamination. The critical parameters that might affect the quality of the finished product should be identified during product development. To succeed this, the manufacture process should be classified into individual steps, and each step must be assessed (e.g. on the basis of knowledge or theoretic thoughts) [27].The criticality of these parameters should be determined through a "worst-case" challenge where possible. Prospective validation must be done in accord with a validation protocol which must include some important details such as a description of the process; a description of the experiment; details of the equipment and facilities to be used together with its calibration status; the parameters to be monitored; the samples to be taken (where, when, how, how many and how much); the product performance characteristics/attributes to be checked, together with the test methods; the satisfactory limits; time programs; workforce's tasks; and details of methods for recording and assessing results, including statistical analysis. All equipment, the production environment and analytical testing methods to be used must have been completely validated (e.g. during installation qualification (IQ), and operational qualification (OQ). So that the manufacturer shall to calibrate devices, validate process, control the critical parameter to have the expected quality for his product [28].

Critical parameter to be verified / validated per each process

The critical parameter summarized in the below table to illustrate the parameters which has the high effect on the validity of the process and due to good or bad quality of final product as shown in Table (3).

Table 3: Critical parameter to be verified / validated per each process

Process	Critical parameter	Limits / Acceptance criteria
SPF	source of egg	non-vaccinated and non-infected flocks,
	dirty eggs	dirty eggs must be excluded
	unfertile ratio	should be not more than 1%
	shipping	temperature-controlled vehicles (15-18 °C).
	storage	maximum one week at 13-21°C and relative humidity 70–80%
	freedom from extraneous agent	Certificates for freedom of extraneous agents
Egg and incubator disinfection	concentration of disinfectant	not less than MIC of disinfectant according the certificate of analysis (COA). disinfection by 0.1% chloramine B solution or wiped with a 70% alcohol solution
	water hardness	water hardness not more than 1000 ppm.
	temperature	temperature at 37°C
Incubation before inoculation	incubation time	7-11 day before inoculation according to the virus
	incubator temperature	temperature 37-39 °C
	humidity	60 - 65%
	fan speed	suitable to adjust temperature and humidity
	ventilation ratio	suitable to adjust temperature and humidity
	temperature distribution	temperature distributed well in the incubator confirmed by data logger
	Egg turning	eggs should be turned three times/day
	egg candling	in a darkened room or area shielded by curtains. infertile eggs, early deaths and late deaths must be discarded
Inoculation	transferring of working seed bank to inoculation area	on ice box
	inoculum certificate	passed quality control testing and certificate is issued
	titer of working seed	high titer not less than 2^s/25 µL
	inoculation route	according to the virus
	Inoculation dose	0.1 mL/ egg
	man power hygiene	class A
Incubation after inoculation	time of incubation	according the virus type
	incubator temperature	temperature 37-39 °C
	Humidity	60 - 65%

	fan speed	suitable to adjust temperature and humidity
	ventilation ratio	suitable to adjust temperature and humidity
	temperature distribution	temperature distributed well in the incubator confirmed by data logger
	egg turning	should be not turned after inoculation
Egg chilling	Temperature	15 °C for 24 h
	sanitization of cold room	disinfection by 0.1% chloramine B solution or wiped with a 70% alcohol solution
Decapping / Harvesting	sterile tools	sterile tools
	area classification	class A
	needle sterility	sterile tools
	harvest volume /egg	9-10 ml
	antibiotic and its concentration	according to SOPs
	man power hygiene	technicians should wear clean laboratory coats, clean hair covers, facemasks, sterile gloves after scrub their hands with an antimicrobial soap
Inactivation	type of in-activator	according to in activator (formalin, BEI or beta-propiolacton)
	concentration	according to inactivation kinetics
	temperature	according to the inactivator and inactivation kinetics
	pH	according to the inactivator
	area classification	area class A
	neutralization of inactivator	according to the inactivator
	man power hygiene	technicians should wear clean laboratory coats, clean hair covers, facemasks, sterile gloves after scrub their hands with an antimicrobial soap
Sampling by QC	time of sampling	before and after the critical processes, sterile tools, sterile containers
Storing in Quarantine	identification of antigens	full details including virus name, batch No., production date, inactivation method
	quarantine store	separated from the released and rejected
	access controlled	only authorized person have access, production is not allowed to reach
Releasing / Rejecting	releasing / rejecting document	QC certificate, officially certificate with the test, acceptance limit, Pass/ Fail result, labels be changed to released / Rejected
Formulation, filling, storing	under controlled condition	According the company procedures and international regulation

Conclusion

The inactivated vaccine production is very complicated process, has many stages and a lot of critical parameters which need continuous monitoring to be under supervision. Validation of all these critical parameters has the great impact on defects, nonconformance decreasing and processes improvement.

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