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Environment Monitoring, Result Evaluation and Common Contaminants Study of Vaccine Manufacturing Facility

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Abstract: ***Assurance of the sterile manufactured products can be given by carefully designed and executed environmental monitoring (EM) program. State of control in an aseptic manufacturing process reveals one of the most important factors that is environmental monitoring. For the release of the sterile production batch/ in the sterile product release process or procedure, environmental monitoring results are decision making consideration. Environmental monitoring describes the microbiological testing undertaken in order to detect changing trends of microorganism's growth within the clean rooms or controlled environments. Satisfactory results of the environmental monitoring provide the consistent and successful performance of the physical construction of the cleanroom, Heat ventilation and air conditioning (HVAC) system, personnel behaviour and performance in cleanroom, aseptic and clean gowning practices, equipment, aseptic and cleanroom operations. Veterinary vaccine manufacturing facility consists of various virus strains, bacterial cultures and tissue cultures in same premises. The objective of the present work was to perform the environment monitoring of the veterinary vaccine manufacturing facility using the various sampling methods, to identify the environment isolates by morphological and biochemical tests which could be either normal or any abnormal novel flora found in the environment of the veterinary vaccine manufacturing facility which could hamper product quality drastically and to prepare the common environment isolate data bank to use as a guide to keep the environment under control as per regulatory requirement for the veterinary vaccine safety, integrity, strength, purity and quality.***
Keywords: EM, Environment Monitoring, Contamination, Cleanroom

I. INTRODUCTION

The Indian veterinary vaccine market has reached 107 million dollar in 2011 and its forecast to reach 174 million dollar by 2020 with a CAGR of 5%[1]. Veterinary vaccines fall in the category of the schedule C & C1 of the Drugs and Cosmetic Acts 1940, Biological and Special Products, so these products must be manufactured under the cGMP manufacturing facility [2]. Indian Pharmacopeia published in 2018 contains total 14 number of veterinary monographs along with the other monographs by the joint efforts of Indian Federation of Animal Health Companies (INFAH) and Indian Pharmacopeia commission (IPC) to have the standards for veterinary drugs shall as goods as human drugs.

Veterinary vaccine formulations are sterile parenteral formulations in which environment monitoring plays critical role in maintenance of the sterility assurance level of the vaccine product manufactured. For veterinary vaccine industry, sterile product batches are wasted and the plant shutdowns when microbiological contamination occurs. Such contamination leads to loss of invested money, time of manufacturer, product delays, shortages or unavailability and loss of customer's confidence. The microbiological quality of drugs and biologics is very necessary for their effectiveness and end user's safety. Additionally, microorganisms can change the composition and pharmacology of drugs with adverse effect on their effectiveness due to the breakdown of active ingredients as well as on their safety due to the toxicity of potential degradation of products. There are substantial evidences including the warning letters, alert notifications and failures establishing a direct relationship between the level of environmental control and the final quality of the product environmental control is a major concern in sterile vaccine manufacturing.

It is challenging task to have the efficient design of the environment programme, execution of the programme, evaluation of its results, to understand the trend of the normal and abnormal microorganism, to have the data bank of the environment isolates for control reference. In this article we have selected one of the aseptic areas of the veterinary vaccine manufacturing facility for which environment monitoring programme was executed. Different sampling techniques at various frequencies were used and results were observed and evaluated from the environment monitoring.

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According to the FDA (Food and Drug Administration) guidance for industry, viable monitoring is to be done where highest risk of the contamination to the product exists. Therefore clean rooms and clean air devices should be routinely monitored during operation. Environmental monitoring locations must be based on risk assessment and the results obtained during the classification of rooms [3].

One must be aware about the potential sources of contamination in the environment to find out the location for the environment study and to make trend for such microorganisms [4].

II. MATERIALS and METHODS

For the study of common contaminants in aseptic area for the environmental monitoring filling area from vaccine manufacturing site was selected. Filling line is located in grade A under LAF surrounded by Grade B , Grade C and Grade D corridor subsequently for liquid solution filling into vials for Lyophilization process [5].

III. SAMPLING FREQUENCY and SAMPLING METHODS

Table I Environment monitoring frequencies for filling area [5].

Frequency Of Sampling In Dynamic Condition	Area Class
During Full Operation	Grade A (Filling Operation)
Daily	Grade B, Laminar Air Flow Work Stations in B
Frequency Of Sampling In Static Condition	Area Class
During Full Operation Once Per Shift by Volumetric, Settle Plate, Contact Plate and Glove Print	Grade A (Filling Operation)
Daily	Grade B
Once Per Shift By Volumetric, Settle Plate, Contact Plate and Glove Print	Laminar Air Flow Work Stations in B

1) *Active air Sampling:* Active air sampling was done by the Air sampler, AES laboratories make, model AESAP1075, using SCDA (Soyabean casein digest agar) plates. In air sampler, air sample is to be drawn through slits and to agar surface and by controlled air flow, maximum impingement of air sample from various location is done. After completion of air sampling, plates were incubated for 72 hours at 20-25 ^{o}C and then for 48 hours at 48 hours at 30°C - 35°C. Colonies were counted and recorded whereas observed [6].
2) *Passive air Sampling:* Passive air sampling was done by settle plates petri dishes containing SCDM (Soyabean Casein Digest agar Medium). Plates were opened and exposed for not less than 4 hours where lids of dishes were removed. After completion of exposure, petri dishes were covered with lids, sealed with parafilm and send for incubation. Incubation of the petri dishes were done for 72 hours at 20°C - 25°C and then for 48 hours at 30°C - 35°C. Colonies were counted and recorded whereas observed[7].
3) *Contact Plate Method:* Surface sampling was performed with raised RODAC plates. Before testing any surface, it was to be ensured that the area was dried. Contact plate were pressed onto the area in maximum contact site for 10 second by applying a constant gentle force spread evenly over the whole contact plate without sliding and avoiding the creation of bubbles. After contact with sample replace the lid and the area tested had been wiped down with isopropyl alcohol 70% to remove any residue left by the contact plate. The contact plates were placed for 20°C - 25°C and then for 48 hours at 30°C - 35°C[8].
4) *Swabbing Method:* Swab samples were collected by removing a sterile swab from a sterile tube. The selected surface was swabbed by moving the swab back and forth across the surface with several strokes at angle of 45 degree. The swab was rotated during sampling to ensure that the entire surface of the swab was used. After sampling, the swab returned to its pre labelled sampling tube containing liquid media. Swabs media was incubated at 20°C - 25°C and then for 48 hours at 30°C - 35°C.
5) *Finger Dab:* TSA (tryptone soya agar) used which was pre incubated for 48 hours. Before performing the test the operator was ensured that the gloves were dried. Right/left finger with gloves of operator was placed on the surface of the plate firmly and gentle pressure was applied for 5-10 seconds. The plates were closed and fingers were sanitized with sterile 70% isopropyl alcohol. The plates were placed for 20°C - 25°C for 72 hours and then for 48 hours at 30°C - 35°C[9].

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IV. STUDY of the ENVIRONMENT MONITORING COMPRISE of

A. Selection of location in Modules & corridor via risk assessment
B. Protocol for the environmental monitoring.
C. Study the personal qualification for working in aseptic area.
D. Prerequisites for environmental monitoring as Media Procurement, Media testing, Media Preparation and Media Incubation.
E. Execution of the environmental monitoring as per protocol
F. Environmental monitoring trends, observations and results.
G. Identification of the environmental isolates and data bank for the isolated microorganisms including their common EM existence, effective disinfectant against them.
H. Conclusion of the study.

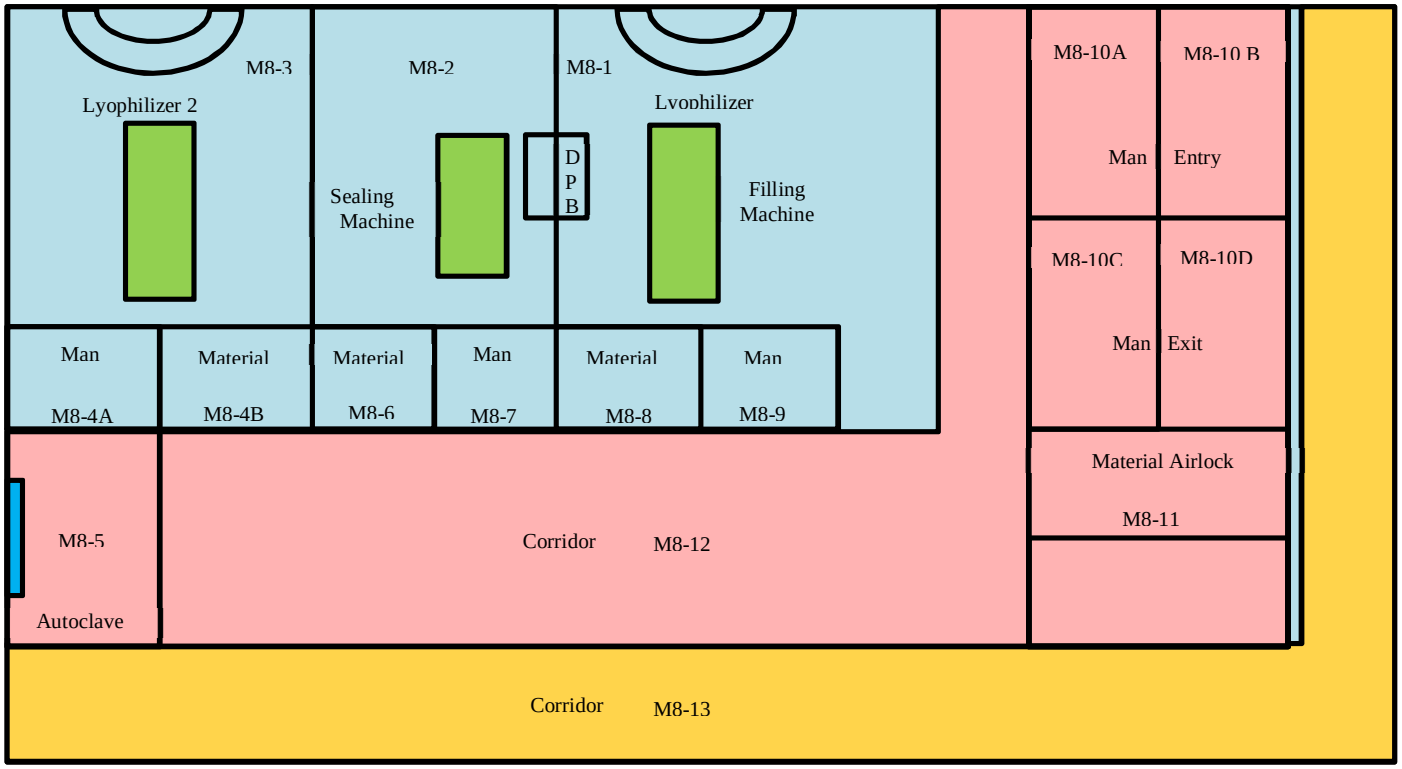

Fig. 1 Schematic Layout of the Vaccine Filling area for Environment Monitoring

Table II Details of the Sampling Locations with Justification for Selection and Rational for Number of the Locations in Filling Area[10].

Area	Room	Class	Area(M^2)	No. of Locations	Rational	Justification
Filling and freeze drying room	M8-1	A	6.78	4	1. Front side near filling needle 2. Back side near filling needle 3. Front side left near working 4. Edge of the filling machine near turn table	o Near filling Machine there is maximum chance of the contamination by operator intervention.
		A	2.86	2	1. Front side right near working 2. Edge of the Filling Machine near collection unit	o Near filling machine there is maximum chance of the contamination by operator intervention.
		B	23.53	6	1. Near man entry 2. Near return riser 1 3. Near return riser 2	o Near filling machine there is maximum chance of the contamination by operator

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Area	Room	Class	Area(M^2)	No. of Locations	Rational	Justification
					4. Near filling station outside LAF right side 5. Near filling station outside LAF left side 6. Near Lyophilizer loading side	intervention. o Maximum chance of the contamination near return riser. o Near Lyophilizer loading maximum man intervention occur so maximum chances of contamination over there.
Person airlock of filling room	M8-9	C	6.44	4	7. Near entry door 8. Near return riser 9. Right hand right corner 10. Right hand left corner	o Maximum chance of the contamination near return riser as it swipes out the contamination from clean room.
Material airlock of filling room	M8-8	C	4.39	3	1. In front corer 2. Right hand right corner 3. Right hand left corner	o Maximum chance of the contamination near return riser as it swipes out the contamination from clean room. o In grid fashion one location in each section so to cover uniformly overall area.
Person Airlock1	M8-10a	C	4.00	2	1. Near entry door 2. Near return riser	
Person Airlock2	M8-10b	C	4.00	2	1. Near entry door 2. Near return riser	
Person Airlock3	M8-10c	C	4.00	2	1. Near entry door 2. Near return riser	
Person Airlock4	M8-10d	C	4.00	2	1. Near entry door 2. Near return riser	
Material airlock from corridor	M8-11	C	8.41	6	1. Near material entry door 2. Near return riser 3. Entry side right corner 4. Entry side left corner 5. Exit side right corner 6. Exit side left corner	
Module corridor	M8-12	C	36.14	10	1. In grid fashion. 2. Entrance left side Four corner. 3. Near return riser left side 4. Near return riser right side 5. Right side four corner.	o In grid fashion one location in each section so to cover uniformly overall area as it is less critical area. o
Corridor	M8-13	D	40.15	10	1. In grid fashion. 2. Entrance left side Four corner. 3. Near return riser left side 4. Near return riser right side 5. Right side four corner.	
DPB	M8-1	A	0.38	1	In centre	o DPB is small in size at centre one location is sufficient to represent whole area of DPB.

M^2: Meter square, M: Module room, LAF: Laminar Air Flow, DPB: Dynamic Pass Box,

V. ISOLATION OF MICROORGANISMS

Media are source to supply nutritional and growth requirement of microorganisms. From the environment monitoring study, microorganisms are isolated and cultivated on selective medium based on their respective morphological and microscopic characteristics.

Colony characteristics and Gram staining were done and as per the Gram staining's results, plates were inoculated from the previous growth on the plate during environment monitoring activity for 72 hours at 20-25 ^oC and then for 48 hours at 30°C - 35°C. Isolated colony cultures was streaked on selective and enrichment medium for differential growth of the microorganisms. Biochemical test were performed for all indivual isolated microorganism.

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Enrichment media used are chocolate agar & Blood agar. Selective media used are Phenyl ethyl alcohol (PEA) agar, Mannitol salt agar, MacConkey agar, Eosin methylene blue agar. Differential media used are Mannitol salt agar, MacConkey agar, Eosin methylene blue agar.

VI. CULTURAL CHARACTERIZATION [11]

Microbial growth found on plates was examine in the form of colonies. Surface of this colonies had specific characteristics. In cultural characteristics features of the colony as appearance, size, shape, margin, elevation, consistency, texture, opacity, pigmentation were observed and recorded.

VII. COLONY MORPHOLOGICAL CHARACTERIZATION [12]

Gram staining study is one of the most versatile and used technique for the morphological characteristic of the microorganisms. In the gram staining heat fixed smear of the culture was prepared and stained with crystal violate solution. After staining Gram's iodine was added. Slide was then rinsed with tap water and washed with the decolorizing solution to remove the excess crystal violet from slide. Finally slide smear was stained with safranin for 45-60 seconds, rinsed with tap water, dried and examined.

VIII. BIOCHEMICAL TESTS for STUDY of BACTERIAL METABOLIC ACTIVITIES[13]

1) *Carbohydrates Fermentation Test:* Inoculated a loopful of culture in to sugar broth and incubated at 37°C for 24 hours. Acid and gas production would observe if bacteria do carbohydrate fermentation.
2) *Methyl Red Test:* Test culture was inoculated in glucose phosphate broth and incubated at 37°C for 48-72 hours. After incubation few drops of methyl red indicator to the medium were added and the development of the red colour was observed if bacteria produce acid.
3) *Voges-Proskauer Test:* Test culture was inoculated in glucose phosphate broth and incubated at 37°C for 48-72 hours. After incubation 0.6 ml of α-napthol and 0.2 ml of KOH solution per ml of culture broth was added. Red colour developed in the tube after shaken confirmed the generation of the acetyl methyl carbinol form sugar if there.
4) *Citrate Utilization Test:* Colour change of the slant was observed after incubation of the citrate agar plant on which the streaking was done and incubated at 37°C for 24-48 hours. If bacteria utilized the citrate then they had released ammonia which would convert green colour to blue.
5) *Indole Production Test:* 4-Dimethyl amino benzaldehyde which is Ehrlich's reagent produce red colour compound if bacteria produce Indole by reaction. Tryptone broth was inoculated with loopful of test culture, incubated at 37°C for 24 hours and xylene was added to separate Indole and then addition of 1ml Ehrlich's reagent was added slowly so as to form the layer on the surface of xylene to have red colour compound.
6) *Hydrogen Sulphide Production Test:* If the bacteria produced sulphur compound and produced hydrogen sulphide which would react with the lead acetate paper and produce black colour of strip. For that 2% peptone broth was inoculated with loopful test culture and lead acetate paper strip was placed at the neck of the tube pass through the cotton plug and upon incubation at 37°C for 24 hours colour change of the lead acetate paper strip was observed.
7) *Urea Hydrolysis Test:* If the bacteria utilized urea they would produce the ammonia and carbon dioxide from it. For that urease broth was inoculated with a loopful of test culture and incubated at 37°C for 24 hours with the phenol red indicator. Upon incubation orange colour was converted into pink if bacterial produced ammonia and carbon dioxide.
8) *Nitrate Reduction Test:* If bacteria reduced the nitrates then upon inoculation of peptone nitrate broth with a loopful of test culture, incubated the medium at 37°C and addition of 0.5 ml of the reagent A (α-naphthylamine reagent) and B (sulphanilic acid reagent) each to the test medium would produce red colour compound within 30 second.
9) *Ammonia Production:* Peptone nitrate broth was inoculated with loopful test culture and red litmus paper strip was placed at the mouth of the culture tube, upon incubation at 37°C for 24 hours, colour of the red litmus paper changed from red to blue.
10) Starch Hydrolysis Test: If bacteria had hydrolysed the starch they would produce the brown colour with the reaction with the Logon's iodine. For this test, test culture was inoculated on the agar plate and incubated at 37^{o}C for 24-72 hours. Transplant zone surrounding the colony was flooded with Logon's iodine and blue colour faded rapidly.
11) *Casein Hydrolysis Test:* Inoculated the test culture on the skim milk agar plate as spot or line and incubated at 37^{o}C for 24 -48 hours. It was observed for a clear zone of casein solubilization surroundings the growth of organisms. If casein was hydrolysed then plate having the clear zone and if casein was not there then there was white colour zone due to casein.

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12) *Gelatin Hydrolysis Test:* Inoculated a loopful of test culture into one of the tubes and the second tube was left uninoculated (control) containing gelatin as substrate. Incubated both the tubes at 37°C for 24-72 hours. After incubation both the tubes were placed at 5-10 °C in refrigerator for 30-60 minutes. After refrigeration, if liquefaction of gelatin would take place it confirmed the presence of the gelatinase enzyme.
13) *Lipid Hydrolysis Test:* After inoculation of the test culture on the agar plate containing tributyrin as lipid substrate and incubated at the 37°C for 24-72 hours, if clear zone of calcium carbonate solubilization was observed indicated bacteria hydrolyse lipid and if colour would remained intact then it indicated no lipid utilization by bacteria.
14) *Catalase Test:* If bacteria possessed small amount of catalyse upon the additional of the hydrogen peroxide to the bacterial isolates then oxygen would evolved. For this test a loopful of the test culture was inoculated in to the broth tube and incubated at 37°C for 24-72 hours. After incubation, 1 ml of hydrogen peroxide was added over the growth in broth. Effervescence of oxygen confirmed the presence of catalase.
15) *Oxidase Test:* In this test if the cytochrome oxidase is present then it catalyse the redox reaction between bacteria and dye (tetramethyl-p-phenylenediamine dihydrochloride), so dye will reduce and deep violet colour is produced. Test organism was grown on nutrient agar medium for 24 hours and filter paper strip was moisten with 3-4 drops of tetramethyl-p-phenylenediamine dihydrochloride solution. Smear on filter paper with the help of sterile wire loop was made which showed formation of violet colour after 10-15 seconds if oxidase would present.
16) *Coagulase Test:* Coagulase enzyme converts the soluble fibrinogen into insoluble fibrin which is used for identification of the Coagulase positive and negative *S.aureus* bacteria. A well isolated colony was taken from the plate and a dense suspension was prepared. A drop of thick suspension on slide was placed and loopful of oxalated plasma was added to a thick bacterial suspension and stirred well. Clumping of cells within 5-10 seconds observed if coagulase would present.

IX. RESULTS & EVALUATION

1) *Results of the settle plates cunts*, swab samples, contact plates and finger dabs obtained are as mentioned in table III to VI respectively and in figure no.2.

Table III OBSERVATIONS for SETTLE PLATE TECHNIQUE

Class	Limit for bacterial growth (CFU/m^3)			Limit for fungal growth (CFU/m^3)		
	Alert level	Action level	Result	Alert level	Action level	Result
Class A	Nil	1	Nil	Nil	1	Nil
Class B	>1	10	1	Nil	1	Nil
Class C	10	100	3	Nil	1	Nil
Class D	50	500	11	Nil	1	Nil

CFU: Colony Forming Unit

Table IV Observations For Surface Monitoring Using Swab Technique

Area	Limit	Result
Laminar air flow	0	Nil

Table V Observations For Contact Plates Using Rodac Plates

Area	Alert level	Action level	Result
Left forearm	N/A	<1	Nil
Right forearm	N/A	<1	Nil
Chest	N/A	<1	Nil

Table VI Observations Of Finger Dab Test

Class A	Alert level	Action level	Result
Right hand	N/A	<1	Nil
Left hand	N/A	<1	Nil

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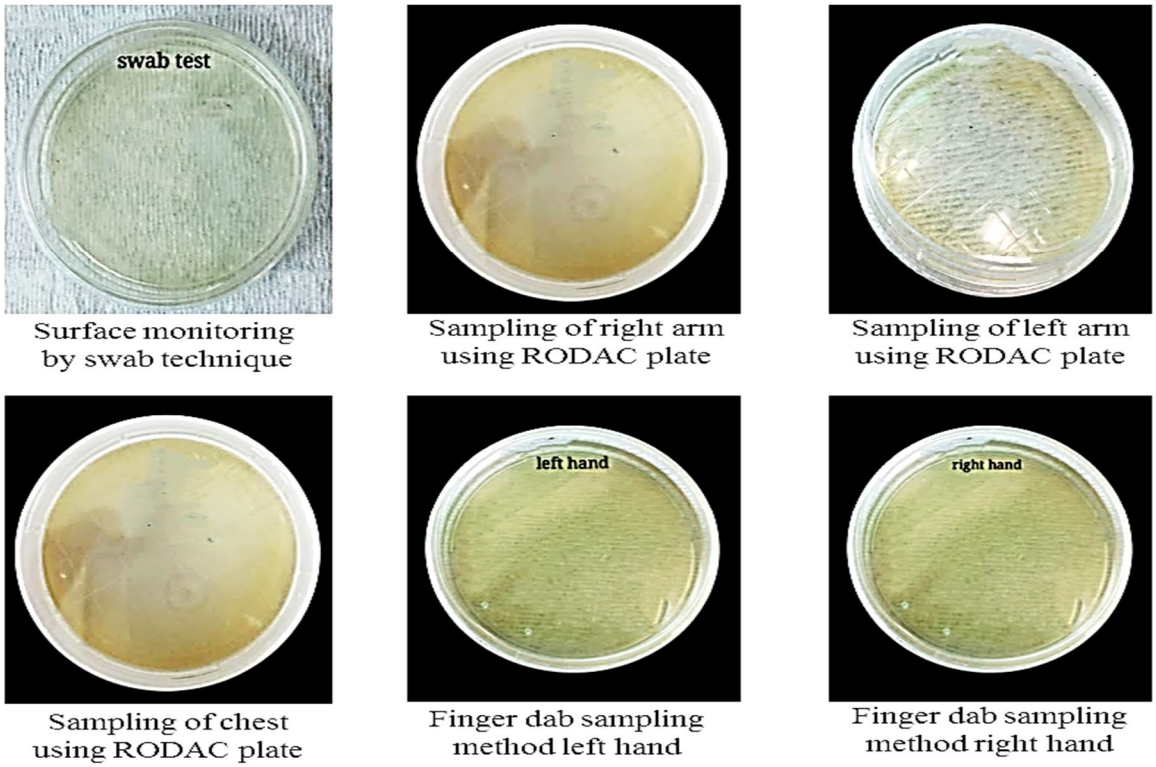

Fig 2 Observations of the Swab & Contact plates

2) Results of the Cultural Characteristics

Table VII Observations Of Colony Characteristics

Characters	Colony1	Colony2	Colony3	Colony4	Colony5
Size	Intermediate	Large	Large	Intermediate	Intermediate
Shape	Round cocci	Irregular rods	Irregular rods	Round cocci	Round cocci
Margin	Entire	Undulate	Undulate	Entire	Entire
Elevation	Convex	Umbonate	Raised	Convex	Raised
Surface	Smooth	Dry	Smooth	Smooth	Smooth
Consistency	Butyrous	Wet	Moist	Butyrous	Viscous
Opacity	Opaque	Opaque	Opaque	Opaque	Opaque
Pigment	Bright yellow	White	White	Golden brown	White
Arrangement	In pair, in tetrads	Single, in chain	In chain	In cluster, single	In cluster, in pair
Gram's staining	Gram positive	Gram positive	Gram positive	Gram positive	Gram positive

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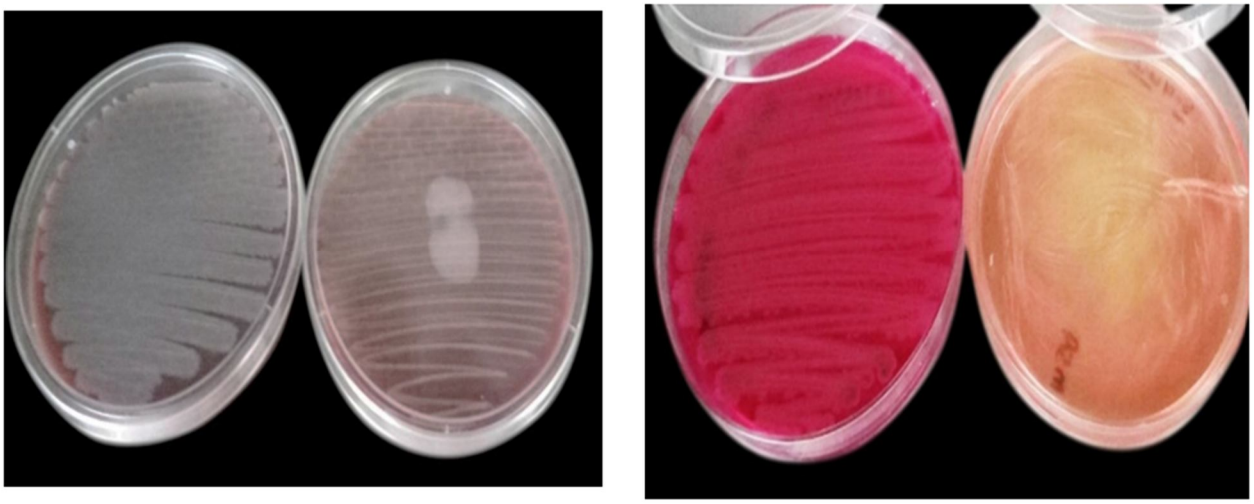
3) Results of Biochemical Tests: Five isolated species have different types of metabolic activities vary in their ability to hydrolyse large molecules like carbohydrates, fats, and proteins as in table 8.

Table VIII Biochemical Characterization Of The Bacterial Isolates [14]

Biochemical properties	Colony1	Colony2	Colony3	Colony4	Colony5
Sugar utilization	-	+	+	+	+
Methyl red test	-	-	-	-	-
Voges-Proskauer test	-	+	+	+	+
citrate utilization test	+	+	+	-	-
Indole production test	-	-	-	-	-
H2S production test	-	-	-	-	-
Urea hydrolysis	-	-	-	+	+
Nitrate reduction	+	+	+	+	+
Ammonia production	-	-	-	-	-
Starch hydrolysis	-	+	+	-	-
Casein hydrolysis	-	+	+	+	-
Gelatin hydrolysis	+	+	+	+	+
Lipid hydrolysis	-	-	-	-	-
Catalase test	+	+	+	+	+
Oxidase test	+	-	+	-	-
Coagulase test	-	+	-	+	-
Haemolysin production	+	-	+	+	-

H2S: Hydrogen Sulphide, + : Positive result, - : Negative result



(1) (2) (3) (4)

(1) Isolate 5 gives white colour colonies on chocolate agar plate. (2) Isolate 1 gives yellow colour colony on chocolate agar plate. (3) Isolate 5 gives pink colour colonies on MSA (Mannitol salt agar) plate. (4) Isolate 1 gives yellow colour colonies on MSA (Mannitol salt agar) plate.

Fig 3 Results of growth on selective media

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X. COMMON DATA BANK OF ENVIRONMENTAL ISOLATES [15]

Table IX Data Bank of the Environment Isolates

Name of Organism	Characteristic	Common Existence	Morphology	Microscopy	Sensitivity against disinfectant
Micrococ-cusleuteus	Gram positive round shaped	Exist normally in human or animal skin.	Circular yellow small colonies	Tetrads and in pair structure	o Phenolic compound o 1%sodium-hypochlorite o 70%alcohol o Formaldehyde o Iodine o Glutaraldehyde
Bacillus subtilis	Gram positive rod shaped	Exist normally in upper layer of the soil	White Large colonies	Long chain and single structure	o Glutaraldehyde o Iodophore
Bacillus cereus	Gram positive rod shaped	Exist normally in soil, dust and plant	White large colonies	Chain Structure	o Glutaraldehyde o Iodophore
Staphylococcus aureus	Gram positive round shaped	Exist normally in normal skin flora and lower reproductive tract of women.	Golden- yellow large colonies	Grape like clusters	o Ethanol o Quaternary ammonium
Staphyloc-occus Epidermis	Gram positive round shaped	Exist normally in normal skin flora and lower reproductive tract of women. In the nostrils	Golden- yellow large colonies	Grape like clusters	o Ethanol o Quaternary ammonium

XI. DISCUSSION & CONCLUSION

Environmental Monitoring of the filling area of the veterinary vaccine manufacturing plant where various virus strains, bacterial and tissue cultures were handled, was done. Morphological, microscopical and biochemical tests were conducted to identify the microorganism. By growth on the selective media from the contaminants, microorganisms were *Micrococcus luteus, Bacillus subtilis, Bacillus cereus, Staphylococcus aureus, and Staphylococcus epidermis* confirmed.

Results of the environmental monitoring reveals that in Grade A and Grade B, CFU count obtained was zero which indicates the compliance of the filling operation environment with the regulatory requirements and all the systems including HVAC and procedural controls are sufficient to control the contamination to the fill finish product. Environmental Monitoring of the Grade C & Grade D shows the CFU count under the acceptance limit.

All the identified microorganisms are commonly existed from the human being and they may carry over from the persons engaged in the activities and are common pharmaceutical microorganisms which provide the basis for the risk assessment for products and environments. Reviewing the results of the environment monitoring programme, it was recognised that no novel or abnormal microbial flora existed. To maintain the good control over these common contaminants in area, constant good aseptic training to the persons engaged in the aseptic operation and effective sanitization programmer is to be done. All the identified and isolated microorganism culture is preserved as the data bank for the common environmental isolates and same will be used as reference in future for environmental study.

XII. ACKNOWLEDGEMENT

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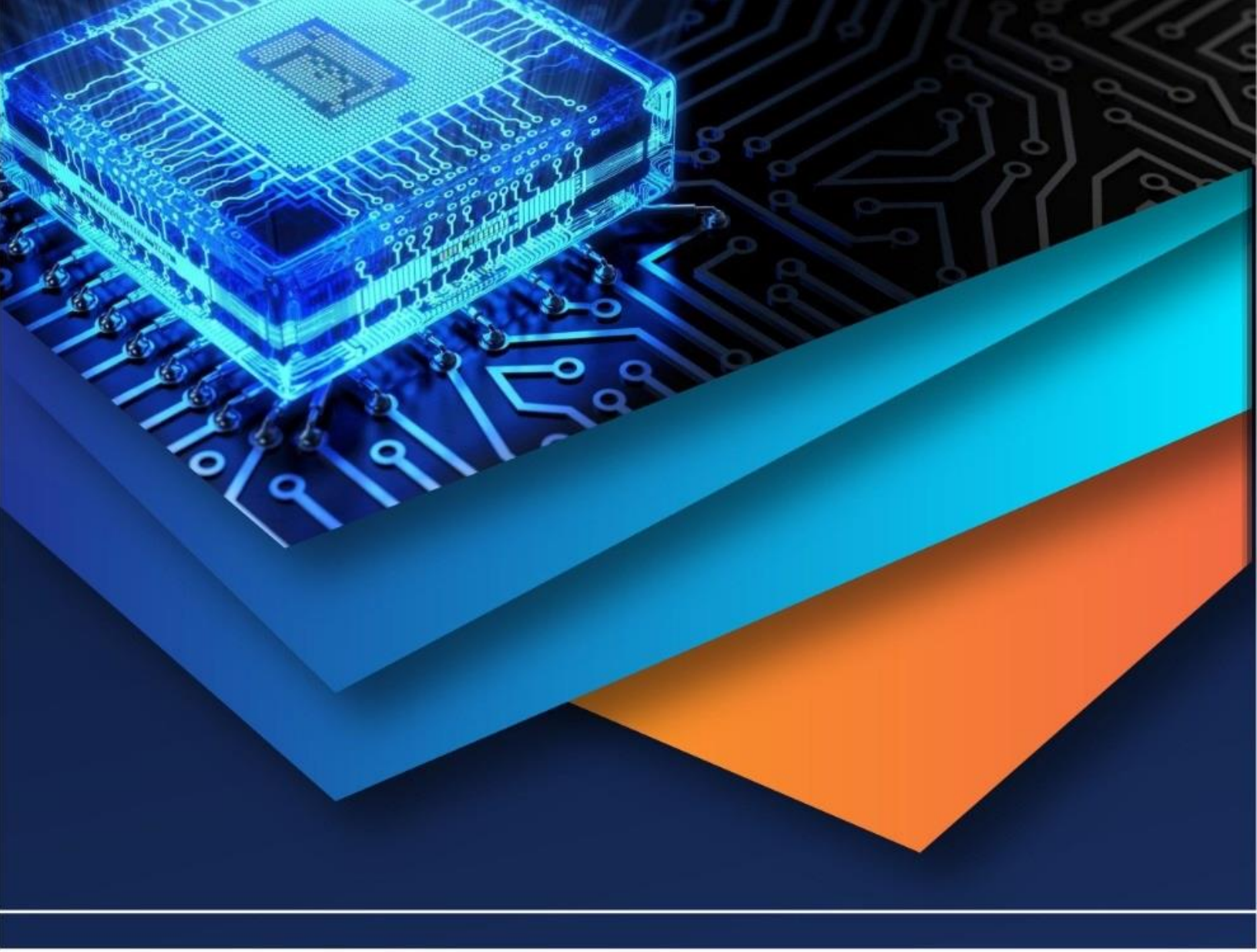

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