Online Non-Viable Particle Count Sampling Location

Risk Analysis Protocol

Risk Analysis Protocol for Online Non-Viable Particle Count Sampling Location

1.0 Document Approval:

PREPARED BY:

Vendor Name	Name	Designation	Sign/Date

REVIEWED BY:

Dept.	Name	Designation	Sign/Date
Quality Assurance			
Engineering			
Production			
Microbiologist			

APPROVED BY:

Dept.	Name	Designation	Sign/Date
Production Head			
Quality Assurance			
Engineering Head			
QA Head			

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2.0 Revision History:

Document Name	Revision No.	Date Issued	Details

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3.0 PURPOSE:

This study or risk assessment/analysis will be performed or for …… Facility of customer, where they are installing new SCADA based system for Monitoring of Non-Viable Particle Counter and Viable Sensors. This analysis covers only environmental monitoring of processes associated or related to the aseptic filling process and does not consider any design and technical specifications at all.

4.0 OBJECTIVE:

The scope of this document is to validate critical sampling point for particle counting system for the aseptic process under Grade A and Grade B areas/conditions. Also new sampling point can be added if required based upon risk analysis. Below are the general approach to achieve this.

- Each sampling point has submitted to risk analysis according to the following approach.
- An assessment to determine the "most critical" sampling point that reflect the greater risk to product, containers or closures.
- An evaluation of existing sample points to determine their effectiveness of placement to achieve this objective.
- An assessment performed based on "risk" calculation for product contamination.

5.0 SCOPE:

Scope of this document is applied to assess the risks associated with initiation of improvement projects, change(s) in order to control and/or eliminate potential impacts on the patient, product and the process. The method is therefore applicable to the implementation of Non-Viable Particle monitoring in the ……. at Customer.

6.0 SYSTEM DESCRIPTION:

The particle counter is used to monitor particles in clean room and initiate an alarm when the process goes out of specification and generates unacceptable numbers of particles. The system is used as early identification of possible contamination in critical aseptic area. The critical aseptic area is where critical aseptic process shall be carried out. The particle counting system consist of number of particle counters installed on different location of Grade A and Grade B and monitored centrally using a SCADA based software. The risk analysis includes determination of the appropriate number of NVPC sampling points and their locations.

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7.0 REFERENCES:

7.1 Quality risk Management ICHQ9 Current step 4 version dated 9 November 2005.

7.2 Failure Modes and Effects Analysis Procedures.

7.3 EC Guide to Good Manufacturing Practice – Revision to Annex -1 Manufacture of Sterile Medicinal Products.

7.4 ISO 14698-1 Cleanroom and associated controlled environments – Bio contamination control part 1: General Principal and methods.

7.5 ISO 14698-2 Cleanroom and associated controlled environments – Bio contamination control part 2: Evaluation and interpretation of bio contamination data.

7.6 FDA Guideline for aseptic process (Section IV – Buildings and Facilities and section X- particle Monitoring).

7.7 ISO 14644-1 Classification of air cleanliness.

8.0 RESPONSIBILITY:

……. Private Limited

- Prepares this risk analysis document taking into account the customer recommendations and corrections.
- Works closely with customer team to collect and evaluate of all necessary data to prepare the final report of the risk analysis.
- Submits the document to customer for approval.
- Coordinate with the team involved in the Risk Analysis.
- Perform the formal risk assessment, and proposed the suitable monitoring point for particle count

Concern Department

- Review and approves the methodology used during the analysis.
- Discusses and review the data collected during the risk analysis and approves the results.
- Review and approves the protocol of this Risk Analysis.
- Maintain the risk analysis after implementation of actions to demonstrate the proposed preventive actions have been implemented and are effective to minimize risk.

- To take action to mitigate the risk as identified in the risk assessment report.

Concern Department Head

- To review the Risk Assessment Report.
- Ensure availability of adequate resources for execution of risk assessment.
- Create a cross functional team (CFT) across various function and department and appoint a team leader appropriate to the risk assessment & migrate risk being considered.
- To ensure ongoing quality risk management process operate effectively.

Quality Assurance Department

- To review and approve the Risk Assessment Report.

QA Head

- To approve the Risk Assessment forms for quality related events.

9.0 DEFINITION OF TERMS:

9.1 Quality Risk Management: An overall and continuing Systematic Process for the Assessment, Control, Communication and review of risks to the Quality of a pharmaceutical Product or medical device across the Product Life Style in order to optimize its benefit-risk balance.

9.2 Risk: The combination of the Probability of Occurrence of Harm and the Severity of that Harm (ISO/IEC Guide 51).

9.3 Risk Acceptance: The decision to accept risk.

9.4 Risk Analysis: The estimation of the risk associated with the Identified Hazards.

9.5 Risk Identification: The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description. Information can use historical data, theoretical analysis, informed opinions and concerns of stakeholders.

9.6 Risk Review: Review or Monitoring of Output/Results of the Risk Management Process considering (if appropriate) new knowledge and experience about the risk.

9.7 Risk Communication: Sharing of information about Risk Management between the Decision Maker and other Stakeholders.

9.8 Risk Control: Actions implementing Risk Management Decisions.

9.9 FMEA : Bottom-up analysis of each potential failure mode in every subsystem to determine its effect on other subsystem and on the function of the system.

9.10 FMECA : Follow-up to FMEA which classifies each effect according to its severity and probability of occurrence.

9.11 Abbreviations:

- FMEA : Failure Mode Effective Analysis
- ICH : International conference for Harmonization
- CAPA : Corrective and Preventive Action
- QA : Quality Assurance
- QC : Quality Control
- RPN : Risk Prioritization Number
- CFT : Cross Function Team
- FMECA : Failure Mode Effective and Criticality Analysis

9.12 Attachment:

Detailed Risk assessment report.

10.0 PROCEDURE FOR RISK ASSESSMENT:

- Team of Risk Management: GMP coordinator and head of concerned department to whom the risk is concern and CFT shall involve in preparation and review of risk assessment document and same shall be approved by QA.
- **Approach to conduct the risk assessment:**

  The approach will be based below methods as under

  - ❖ FMECA-To decide the critical sampling location.
  - ❖ GRID based approach: to decide the sampling probe location.

10.1FMECA Based Risk Assessment:

This risk assessment was structured to anticipate the potential failures (potential presence of non-viable particles and location of the highest risk) in the Aseptic Area (Grade A and B the results of this risk assessment will identify the most efficient preventive/corrective actions to be minimize the failure probability. In the objective to identify the most significant potential failure, the risk assessment is based on the participant's expertise. The potential failure identified, as well as the existing means to prevent or detect the cause of the failure in Aseptic Area Grade A and B, are considered for the implementation and the utilization of NVPC monitoring. The risk have then assessed based on the score for each criteria: Severity, Occurrence, and detection. Assessment of each parameter allows

determination of a RPN (Risk priority Number) for each identified risk for potential NVP monitoring location evaluated.

10.1.1 Severity:

The severity is assessing in function of the consequences that can generate the identified failure. If several consequences are linked to only one failure, the highest score is kept.

10.1.2 Occurrence:

The occurrence is the probability that an identified cause create a failure. Historical data can be used to estimate the occurrence**.**

10.1.3 Detection:

The Detection is based on the probability that the controls in place will allow to observe or detect the failure causes or the failures itself before the patient use. The defined score consists of all the identified controls for a given cause.

11.0 RISK ANALYSIS (STUDY):

Risk analysis based on the attribution of scores associated with an identified risk.

11.1 Risk Analysis – RPN calculation explained in detail:

Note: the selection of "critical" sample point position was based on the calculation of a number that reflects the "risk" to the product (Aseptic process flow) that may be microbiology contaminated. This "risk" was expressed via the risk priority number (RPN) that is based on the following factors:

RPN= (Severity) × (Occurrence) × (Detection)

- The Detection was not applicable because we are evaluating a way of detection.
- In this FMEA approach, the Severity was considered as the impact of the effect of that risk on the product (ultimately) leading to product contamination). For this reason as in this filling line the liquid product is filled aseptically, this valve is considered a constant value high.
- The RPN value is only influenced by the occurrence (Probability) the product will be contaminated. This Probability is represented by 2 independent events:

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- The Probability that the point considered will be contaminated (Psampling) by the surrounding Environment, people and/or equipment.
- The Probability that the contamination present in the contaminated point affects the product and/or the material that will enter in direct contact with the product (Pproduct).
- RPN calculation will become:

RPN= (Psampling) × (Pproduct)

- To evaluate every single Probability, a matrix master was used in which all the risk situations are reported that could result in the contamination of the sampling point and the product.
- For every risk, a value was assigned, which indicates the probability that in such a risk situation the sampling point or the product could become contaminated.
- For both probabilities, the probability Psampling and Pproduct result from the sum of all the risk situation related to each type of probability.
- The higher the RPN value, the higher the criticality of the sampling point for the product contamination.

11.2 Psampling Calculation: Grade A

Every position identified in Grade A based on the factors reported in the following table was evaluated:-

VARIABLE	RISK SITUATION		SCORE
Environment/ Personal/Equipment	**Unidirectional air flow UAF YES= presence/NO = absence**	No	2
		Yes	1
	Probable presence/transit of man and Material handling (for example: settle Plates, wipes, Pliers, gloves , cart with Materials, set-up machine, Interventions, freeze-dryer loading)	High	3
		Medium	2
		Low	1
	Environment for Aseptic processing	Acrylic wall/ Flexible Curtains	3
		Closed RABS	2
		Isolators	1
	Closeness of container/closer/product Sensor/sampling probe from moving machine part, surface	Less than 1 foot	3
		From 1 to 2 feet	2
		Greater than 2 feet	1
	Distance from the return riser	Less than 1 foot	3
		From 1 to 2 feet	2

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VARIABLE	RISK SITUATION		SCORE
		Above 2 feet	1
	Duration of product and primary packing material exposure risk at location	More than 5 min.	3
		From 1 to 5 min.	2
		Less than 1 min.	1
	Closeness of container/closer/product From aseptic activity- working site	Less than 1 foot	3
		From 1 to 2 feet	2
		Above 2 feet	1

The calculation of the Psampling was done adding the score from each risk situation, coming from environmental/personal/equipment.

11.3 Psampling Calculation: Grade B

VARIABLE	RISK SITUATION		SCORE
Environment/ Personal/Equipment	**Distance from the return riser**	Less than 1 foot	3
		From 1 to 2 feet	2
		Above 2 feet	1
	Probable presence/transit of man and Material handling (for example: settle Plates, wipes, Pliers, gloves , cart with Materials,)	High	3
		Medium	2
		Low	1
	Possible execution of manufacturing task (presence and/or transit of people with Activity) For example: set-up machine, Interventions and freeze-dryer loading	High	3
		Medium	2
		Low	1
	Closeness of location/sampling probe from moving machine part, surface	Less than 1 foot	3
		From 1 to 2 feet	2
		Greater than 2 feet	1

The calculation of the Psampling was done adding the score from each risk situation, coming from environmental/personal/ equipment.

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11.4 Pproduct Calculation: For Grade A

Every position identified adopting the factors shown in the following table was evaluated:-

VARIABLE	RISK SITUATION			SCORE
Product/ Material Indirect Contact With the Product	**Possible Presence and/or Transit of material and/or product in direct contact with the product.**	**For example: Empty containers, Open filled containers, closure, Filling needles, bowls and hopper For container and closure, container And closure chutes**	High	3
		For example: partially stoppered Vials, vials in the transfer cart,	Medium	2
		For example: No container in the Area, No material in direct contact with product, unloading and storage of sterile wrapped material under LAF	Low	1

The Pproduct was calculated considering the individual scores each risk situation, coming from the product and/or the material in direct contact with the product.

11.5 Pproduct Calculation: For Grade B

Product parameter is not applicable for Grade B as direct product is not exposing in the Grade B.

11.6 RPN Calculation: For Grade A

For every position, the RPN value was calculated according to the following equation:-

RPN = (Psampling) × (Pproduct)

11.7 RPN Calculation: For Grade B

For every position, the RPN value was calculated according to the following equation:-

RPN = (Psampling)

11.8 Risk Matrix Grade A

RPN No.	Risk Description
7 to **25** (sum of Psampling risk multiplied by sum of Pproduct risk with risk situation at low to medium i.e. 7* = 7 and 13* 2= 26)	**Low risk**
26 to 60 (sum of Psampling risk multiplied by sum of Pproduct risk with risk situation at medium to high i.e. 13* 2 = 26 and 20*3= 60)	**Medium to high risk**

- Every critical location based on RPN calculated was evaluated based on the following:-

- ❖ If 7 ≤ RPN ≤ 25 Low risk point considered non critical/ not representative.
- ❖ If 26 ≤ RPN ≤ 60 Medium to High to risk, sampling point is consider to be critical and routine monitoring is recommended. Further analysis is require.

11.9 Risk Matrix Grade B

RPN No.	Risk Description
4 to **7** (sum of Psampling risk having situation at low to medium i.e. 4 to 7)	**Low risk**
8 to **12** (sum of Psampling risk having situation at medium to high i.e. 8 to 12)	**Medium to high risk**

- Every critical location based on RPN calculated was evaluated based on the following:-
- ❖ If 4 ≤ RPN ≤ 7 Low risk point considered non critical/ not representative.
- ❖ If 8 ≤ RPN ≤ 12 Medium to High to risk, sampling point is consider to be critical and routine monitoring is recommended. Further analysis is require.

11.10 Most Critical Position Evaluation:-

The RPN value obtained was evaluated and compared to the threshold value.

- RPN (priority risk index) identified: X value.
- If RPN < 26: for Grade A and RPN < 8 for Grade B sampling location is Not Critical and sampling is not recommended.
- If RPN ≥ 26: for Grade A and RPN ≥ 8 for Grade B sampling location is Critical and sampling should be recommended further analysis is required for selection the position of sampling probe.

12.0 GRID Based Analysis:

- For each critical point, the Grid analysis will be applied to finalize the probe location as under:
- ❖ Particle count data in each Grid location.
- ❖ Air velocity at location height and flow pattern test data will be considered for finalizing probe location.
- ❖ Physical suitability of the probe placement will be considered

- **GRID METHOD:**
- ❖ Based on critically of location and RPN data grid will be design.

- ❖ Particle count will be perform and evaluate result as per grid profiling.
- ❖ Divide the area of risk in to suitable GRID and at the working height.
- ❖ The sample volume should be measure at least one M3 on each location.
- ❖ Also consider the feasibility of installing the probe.
- ❖ Flow pattern test data will be review during grid proofing.
- ❖ Air velocity to be measured and probe height.

13.0 FINAL REPORT:

- At the end of the risk Analysis, a Final report will be written which outlines the information collected during the protocol execution.
- In the final report the rational for the selection of the sampling point must be documented.
- The final report must be signed and dated by the author(s) from customer and …….. and then must be submitted (with Risk Analysis protocol)to customer.

  The following table provides an overview of the different areas considered in this risk analysis and their associated classification.

Room No.	Description	Grade

Note: Risk analysis will be carried out separately.

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14.0 LIST OF DOCUMENTS:

Document No.	Document Topics	Page No.

15.0 LIST OF EQUIPMENT USED IN STUDY:

Equipment Name	Serial No.	Calibration Due Date

16.0 DEVIATION:

Deviation detail:

Corrective Action:

Acceptable: Yes/No

Justification for Acceptance:

Approved By:

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17.0 RECOMMENDATION:

18.0 CONCLUSION:

19.0 REPORT APPROVAL SHEET:

We the undersigned, certify that we have reviewed this document in its entirety and to the best of our abilities, this document is clear, concise representation of outcome of risk analysis for online Non-Viable particle count sampling location in aseptic processing area customer.

Dept.	Name	Designation	Sign/Date
Quality Assurance			
Engineering			
Production Head			
Microbiologist			