Risk-Based Viable and Non-Viable Monitoring Sampling Plan for Microbial Control Program within ISO 7 Cleanroom

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Abstract *— The project intends to present a site-specific risk assessment in order to design a custom viable sampling plan for a compounding pharmacy, which aseptically prepares patient-specific therapies. Additionally, the project has the objective to streamline the current sampling plan by reducing non-value adding locations. The risk-based approach will consist of a touch point risk assessment and a traffic flow risk assessment during operational conditions. The compounding operations will be observed during operational conditions to identify frequently touched locations and traffic flow. A total of 15 samples derived from the risk assessments and analysis representing an 81.2% of reduction from the current sampling plan.*

Key Terms *— Compounding, Environmental Monitoring Program (EMPQ), Parenteral, Touch Point, Traffic Flow, Viable/Non-Viable.*

INTRODUCTION

The compounded sterile preparations (CSPs) is a practice carried out by a licensed pharmacy which incorporate Good Manufacturing Practices (GMPs) and pharmacy knowledge to produce or compound patient specific therapies. The compounding pharmacy scoped in this project aseptically prepares patient-specific doses of Total Parenteral Nutrition (TPN) and lipid repacks to be administered at hospitals by healthcare personnel. The criticality of the product and conditions of the patients it is intended for, the process requires a robust microbial control strategy to mitigate plausible risks.

BACKGROUND

The scope of this project is limited to the buffer area classified as ISO 7 environment to help identify routes of contamination by tracking personnel during normal production. The ISO 7 Compounding Room is designed to serve as a background to the LAFHs within this room. The risk-based approach will consist of a touch point risk assessment and a traffic flow risk assessment during operational conditions.

The touch point risk assessment is performed to establish by objective evidence the surfaces most often touched by personnel during normal manufacturing process. The sterile compounding operation's contamination risk arises from the fact that it is an operation driven by human interaction. The cleaning processes, order processing and actual compounding require employee manipulations at all times. It is common knowledge that the principal source of contamination in any aseptic environment is the employees. Thus, it becomes empirical to identify the surfaces the employees in the operation frequently touch in order to properly assess the risks of those locations and monitor the environmental monitoring results. In the assessment the potential sources and origins of microbial contamination, potential means of transfer of microorganisms within the cleanroom, microbial contamination risks and locations in the cleanroom which are to be considered in the environmental monitoring performance qualification (EMPQ) will be evaluated.

The traffic flow risk assessment is performed to evaluate flow of traffic through and between cleanrooms during normal production in the compounding process employed in the pharmacy cleanroom. The intention is to identify by objective evidence the areas within the cleanroom in which more activities or traffic takes place. These areas are presumed to represent or have a greater potential for contamination since the traffic flow is expected to increase particle generation and disrupt the airflow

inside the rooms. Traffic flow includes personnel flow, material, component and waste flows.

PROBLEM STATEMENT

The manipulations required to handle and produce compounded sterile preparations pose a contamination risks to the parenteral product. In fact, the pharmacy compounding industry has been under scrutiny since the New England Compounding Center's 2012 tragedy where 64 deaths and 751 injured patients occurred due to contaminated medication [1]. As a result of incidents like this one, the regulatory agencies like the FDA, MHRA and TGA have improved their requirement and guidance while highlighting the importance of risk-based assessments, specifically towards microbial control and sterility assurance.

The USP-NF General Chapter <797> "Pharmaceutical Compounding— Sterile Preparations" describe the conditions and practices to prevent the risks associated that may result in microbial contamination [2]. Since the chapter discloses a general approach, a site specific risk assessment is appropriate to design a custom microbial plan intended to the product and process of the compounding pharmacy.

Additionally to the microbial contamination risk, the room currently has 80 sampling points taken on a weekly basis. This quantity and frequency is considered high compared to the dimensions of the room. This project intends assess the validity to possible reduce the current sampling plan, while providing an environmental monitoring capable of detecting the foreseeable potential risks associated to the compounding process carried out in the pharmacy.

In addition to this evaluation, in projects carried out out-of-scope, product and process performance data with an emphasis on the microbial control aspect will be collected to determine if the current design, manufacturing processes and their associated controls (validation, documentation, EM monitoring, etc) continuously mitigate the failure modes identified in the risk analysis and that could lead to unacceptable harm to the patient/user or could impact a therapy.

METHOD

The ISO 7 Compounding Room is designed to serve as a background to the LAFHs within this room. In this area the pharmacists and technicians temporarily stage the materials required for the working day. The pharmacist coordinates the workload according to the areas to distribute the product and approve manual additions and changes in the setup of the compounder equipment. The technicians perform the staging and sanitizing of materials to be used in the compounding process.

The risk-based approach will consist of a touch point risk assessment and a traffic flow risk assessment during operational conditions. The compounding operations will be observed during operational conditions to identify frequently touched locations and traffic flow. Observation for the touch point and traffic flow risk assessments will occur over a two hour period, two repeat occasions, for the Compounding room since it represents the whole time that an operator will be compounding without breaks. The monitoring period will be from 14:00 to 16:00 since it is deemed as a period in which the compounding personnel is operating continuously over the two hours. For these sessions, a total of four (4) employees shall be present in the cleanroom (one pharmacist and three pharmacy technicians). The proposed strategy represents the common operational team assigned for compounding.

Touch Point Risk Assessment

For the touch point assessment the observers will be documenting all the surfaces touched by the employees in the compounding session, the sum of these surfaces will be quantified as touch points. After observing the compounding session during operational conditions, all the touch points will be quantified and the locations identified within the 95th percentile of the compounding process will be analyzed to be considered in the Environmental Monitoring Performance Qualification (EMPQ).

The touch points identified within the 95th percentile of the final container process simulation data set may potentially be selected as a sample location for the respective classified area. After the touch points are identified an assessment shall be performed to provide a justification/rationale for each sample location which will either (1) identify this location as a sample location or (2) eliminate the sample location to be considered and further assessed in the Environmental Monitoring Performance Qualification (EMPQ).

Traffic Flow Risk Assessment

The purpose of the traffic flow assessment is to evaluate: potential sources and origins of microbial contamination, potential means of transfer of microorganisms within the cleanroom, microbial contamination risks and locations in the cleanroom which are to be considered in the environmental monitoring performance qualification (EMPQ).

For the traffic flow risk assessment the observers will map the path of each element to document the movement over the two hours observed. The personnel, product components, finished product and waste traffic flow will be mapped out over a facility diagram in order to assess the risk associated during the production. Cleanroom locations will be identified to present potentially greater microbial risk based upon the traffic flows. Common routes of movement, Intersections between different routes of traffic, Intersections between the same type of traffic and Entry and exit locations will be used as criteria to identify location's risk. After mapping the traffic flow and identifying the areas with potentially greater microbial risk, a table shall provide a justification of the proposed locations along with criteria for selection of location.

RESULTS

The compounding operation was observed over the planned two hour session, during two consecutive days for a total of four hours. Two observers monitored the compounding operation in order to document all surfaces touched and map the traffic flow on the room layouts. The results of each risk assessment are presented in the sections below.

Touch Point Risk Assessment

The compounding operation was observed over the planned two hour session. All surfaces touched by employees were recorded, quantified and analyzed using a Pareto chart. This type of chart was chosen because it provides a visual analysis to compare frequencies. Table 1 list the touch points recorded per run with an average and criteria to develop the Pareto chart.

Table 1
List of Touch Point Recorded

Compounding Room			Number of Times Touched		
Touch Point Description	Run #1	Run #2	Average Count	Cumulative	Cumulative Percentage
Bin	11	65	38	38	16.6
Paper	5	41	23	61	26.6
70% IPA Bottle	12	24	18	79	34.4
70% IPA Wipe	33	0	17	96	41.6
70% IPA wipes pacl	31	0	16	111	48.4
Syringe	25	6	16	127	55.1
Pen	1	27	14	141	61.2
TPN	0	27	14	154	67.1
Label	0	26	13	167	72.8
Binder	4	15	10	177	76.9
Cart Handle	1	14	8	184	80.2
PT IN Handle	0	14	7	191	83.2
PT IN Button	0	14	7	198	86.3
PT OUT Handle	0	9	5	203	88.2
PT OUT Button	0	9	5	207	90.2
EVA bag overwrap	8	0	4	211	91.9
Table	0	8	4	215	93.7
Vials	7	0	4	219	95.2
Blue Tape	5	0	3	221	96.3
Needle	5	0	3	224	97.4
Phone	0	4	2	226	98.3
Door Handle to Gow	2	0	1	227	98.7
Gloves	2	0	1	228	99.1
Cart	0	2	1	229	99.6
Clinisol	1	0	1	229	99.8
Rack	1	0	1	230	100.0

Figure 1 shows the frequently touched locations during compounding activities were identified as accounting for 95% of all personnel touched locations within the classified areas. These locations represent potential sources of microbial contamination which has the potential to be distributed throughout the cleanroom and represent a risk to the ongoing control of the cleanroom environment.

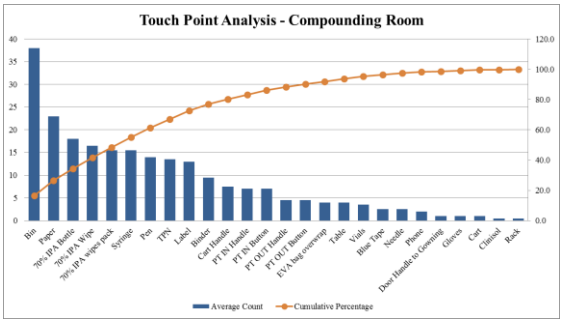

Figure 1
Touch Points Pareto Chart

Table 2 list the touch points accounting for 95% of all personnel touched locations within the classified areas and provides a rationale on which ones to include in the environmental monitoring performance qualification (EMPQ).

Table 2
Touch Point Selection Rationale

Touch Point	Sample Location	Reason for Monitoring Justification / Rationale	Selected as a surface location to be challenged and assessed in the EMPQ?
Compounding Room #133			
Bin	Front side outer surface Back side outer surface	Transfer bins are used for the transfer of materials from the	Yes
Cart Handle	Cart Handle	Cart Handle was observed to be touched multiple time by technicians and pharmacists in the compounding room.	Yes
PT IN Handle PT IN Button PT OUT Handle PT OUT Button	Handle Lock Button Handle Lock Button	The pass through hatches are frequently touched by all cleanroom technicians and pharmacist to move into and out of classified areas. The	Yes
Table	Center of Table	Documentation activities take place on the workbench. Totes and sterile glove may come in contact with the workbench due to the nature of the process and therefore the workbench is categorize as a contamination vector.	Yes
TPN Label	N/A	It is only after the final container has been filled and sealed that	No
Paper 70% IPA Bottle 70% IPA Wipe 70% IPA wipes pack Syringe Pen Binder EVA bag overwrap	N/A	These touch points are components that minimally impact the sterility assurance of the final product. Materials remain within this classified area. In addition, the materials necessary in ISO 5 are sanitized prior entering the LAFHs.	No

The analysis of the touch points resulted in a total of 4 touch points, accounting for 7 sample locations. These are the surfaces that potentially represent a greater microbial risk based on the performed assessment.

Traffic Flow Risk Assessment

After observing the compounding session during operational conditions, the path of the elements scoped in the assessment were mapped. Figure 2 shows the room layout with the traffic flow of each element.

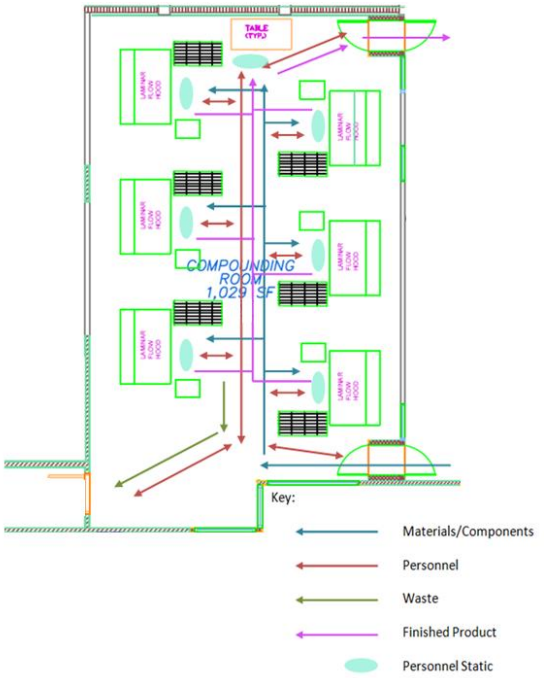

Figure 2
Traffic Flow Map

The mapped traffic flow evidenced that during the compounding process the heavy traffic occurs in the middle section of the compounding room. This is what was expected since the materials are transferred to the room by a pass-through hatch at the lower right side of the layout, then the materials and components are distributed through the Laminar Air Flow Hood cabinets across the room and, finally, the finished product is transferred by another pass-through hatch at the upper right side of the Traffic Flow Map. As a result of this data the following sampling locations were proposed:

- Viable and Non-viable Air near the pass-through IN hatch.
- Viable and Non-viable Air in the middle of the compounding room, between the LAFH #11 and LAFH #15.
- Viable and Non-viable Air in the middle of the compounding room, between the LAFH #16 and LAFH #6A.
- Viable and Non-viable Air in the middle of the compounding room, between the LAFH #14 and LAFH #7A.
- Viable and Non-viable Air near the pass-through OUT hatch.

- Contact plate on floor in the middle of the compounding room, between the LAFH #11 and LAFH #15.
- Contact plate on floor in the middle of the compounding room, between the LAFH #14 and LAFH #7A.

The proposed sampling points can be seen on Figure 3.

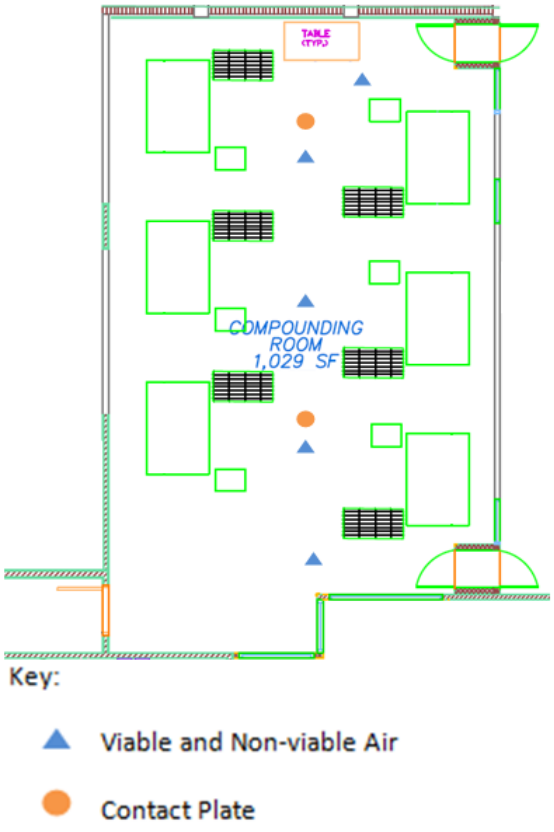

Figure 3
Traffic Flow Map

Similarly to the traffic flow map in Figure 2, the sampling points proposed are concentrated in the middle section of the room, which are to be considered in the environmental monitoring performance qualification (EMPQ). Figure 3 displays the locations to sample with the type of sampling. The viable air sampling is a microbiological sampling performed to the cleanroom air by suctioning the air with centrifugal force. This type of sampling technique allows the operation to detect air quality issues if included in a monitoring program. The contact place sampling method is performed to challenge the surface cleanliness of the selected location.

CONCLUSIONS

The strategy proposed to evidence the surfaces most often touched and traffic flow during operational conditions in the compounding room have been successful to develop a risk-based environmental monitoring program. The assessments reflected the compounding conditions and provided insight to mitigate the risks associated with the operation. The list of the locations derived from the assessments performed represent the points with potentially greater microbial risk. The total samples to be considered in the Environmental Monitoring Performance Qualification (EMPQ) are 15 locations. This represents an 81.2% reduction of sampling locations within the compounding room. This also evidenced that the previous sampling plan was not adding much value since it contained sampling location that were not representative of the actual compounding operation.

RECOMMENDATIONS

The recommendation would be to carry other risks assessments like a process Failure Modes and Effects Analysis (pFMEA) or process risk assessment to possibly identify other sampling locations. If no other locations are added to the list, the locations to include would be the ones listed as follow.

1. Active Air near the pass-through IN hatch.
2. Active Air in the middle of the compounding room, between the LAFH #11 and LAFH #15.
3. Active Air in the middle of the compounding room, between the LAFH #16 and LAFH #6A.
4. Active Air in the middle of the compounding room, between the LAFH #14 and LAFH #7A.
5. Active Air near the pass-through OUT hatch.
6. Contact Plate on floor in the middle of the compounding room, between the LAFH #11 and LAFH #15.

7. Contact plate on floor in the middle of the compounding room, between the LAFH #14 and LAFH #7A.
8. Contact Plate on Bin - Front side outer surface.
9. Contact Plate on Bin - Back side outer surface.
10. Contact Plate on Cart Handle.
11. Contact Plate on PT IN Handle.
12. Contact Plate on PT IN Button.
13. Contact Plate on PT OUT Handle.
14. Contact Plate on PT OUT Button.
15. Contact Plate on Table.

These sampling locations identified will be incorporated into the EMPQ to be performed as part of the overall risk-based Microbial Control strategy.

REFERENCES

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