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Evaluation of Controlled Manufacturing Environments following an Air Handling Unit Shutdown

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This article provides a methodology to evaluate the environmental impact of an air handling unit shutdown in a GMP manufacturing environment.

Environmental control within the biopharmaceutical and medical device industries usually involves a continual cycle of steady state activities interrupted by maintenance and recovery measures. Systems and practices, such as air temperature and humidity control, number of air exchanges, and room cleaning practices, are in place to maintain the overall environmental control. When the environment is challenged or breached, recovery measures are in place to ensure the controlled classified area returns to the qualified state with minimal impact to the environment and product. In many cases, the recovery measures may involve significant cleanings, limited access, and additional environmental monitoring which can reduce manufacturing time and increase cost. This case study evaluated the impact of a short term breach to a biopharmaceutical controlled classified manufacturing cleanroom areas and determined how long it would take these areas to recover with minimal recovery measures and intervention.

Introduction

Air Handling Units (AHUs) are the primary engineering control for classified controlled environments. They provide humidity/temperature control as well as the filtration and air exchanges necessary to ensure an environment meets its classified requirements. These units must be shut down periodically to allow routine maintenance, calibration activities, or planned construction. An example of the activities required to shut down a GMP AHU are listed in Table A.

The average costs associated with AHU shutdowns include two to four planned events annually per unit with an estimated annual cost of $2000 to $4000 per unit for parts and labor. The disruptive impact to the environment can be even longer for unplanned outages caused from mechanical or power failures. An average AHU also has one to two unplanned outages annually. The frequent disruption to the environment, whether planned or unplanned, can have a significant impact to production. These disruptions cause

Activity	Time
AHU Shutdown (Power down)	10 – 15 min
Routine Maintenance Work Performed	30 min – 4 hours
AHU Operation Resumed (Restart)	15 – 30 min
Classified Area Cleaning	2 – 4 hours
Additional Environmental Monitoring	2 – 4 hours
Overall Potential Delay	**Up to 12 hours per AHU Shutdown**

Table A. Typical planned AHU shutdown activities.

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delays in the production schedule due to required area cleanings, additional environmental monitoring, and time and resources necessary to assess product impact if the environmental disruption occurred during manufacturing operations. The degree of the appropriate response to an environmental disruption, especially a short duration of less than a few hours, is needed and data should be generated. This article presents a methodology that evaluated the impact of a temporary AHU shutdown on a classified environment and the potential for an AHU recovery period to minimize recovery efforts, specifically re-cleaning and monitoring of classified rooms.

Case Study Design

Along with climate control, AHUs utilize High Efficiency Particulate Air (HEPA) filters to control the level of particulates, both viable and non-viable, in the environment. An AHU shutdown increases the potential to reach or exceed allowable particulate levels in a controlled environment. To evaluate the potential impact and determine how long it takes for an area to recover with minimal intervention, a study was designed to shut down full scale AHUs for a prescribed amount of time, collect samples, then return to operation and allow the classified environment to recover for a prescribed amount of time. Samples would be collected again following the recovery period. No additional area cleaning would be performed as part of the recovery. The intention was to utilize the study results to temporary AHU shutdowns, whether planned or unplanned.

Industry Requirements

Controlled environments are used to protect products from contamination by greatly reducing the probability that airborne contamination will come in contact with the product or product intermediates or components. Controlled environments are classified based upon their potential impact on product quality. The general industry classifications and criteria[1, 2, 3, 4] utilized for this case study are listed in Table B through Table D.

Classified Manufacturing Rooms

Two different GMP AHUs were selected for the study because they encompassed a range of air classifications (EU Grade B, Grade C, and Grade D) and support both processing and support (non-product) activities. One AHU primarily services Grade D rooms, with an air exchange rate of approximately 20 Air Changes per Hour (ACH), while the other primarily services

EU Grade	ISO Classification	US Designation
A	5	100
B	7	10,000
C	8	100,000
D	Undefined	Undefined

Table B. Area classification.

Classification	Static Conditions[Note A]		Dynamic Conditions[NoteA]	
	≥ 0.5 µm particle/meter^3	≥ 5.0 µm particle/meter^3	≥ 0.5 µm particle/meter^3	≥ 0.5 µm particle/meter^3
EU Grade A	NMT 3,520	NMT 20	NMT 3,520	NMT 20
EU Grade B	NMT 3,520	NMT 29	NMT 352,000	NMT 2,900
EU Grade C	NMT 352,000	NMT 2900	NMT 3,520,000	NMT 29,000
EU Grade D	NMT 3,520,000	NMT 29,000	Undefined	Undefined
Class 100/ ISO 5	NMT 3,520	NMT 29	NMT 3,520	NMT 29
Class 10,000/ ISO 7	NMT 352,000	NMT 2,930	NMT 352,000	NMT 2,930
Class 100,000/ ISO 8	NMT 3,520,000	NMT 29,300	NMT 3,520,000	NMT 29,300
A. No more than (NMT).				

Table C. Particles/non-viable environmental criteria.

Classification	Active Air Sample[Note A]	Settling Plates[Note A]
EU Grade A	LT 1 CFU/meter^3	LT 1 CFU/4 hours
EU Grade B	NMT 10 CFU/meter^3	NMT 5 CFU/4 hours
EU Grade C	NMT 100 CFU/meter^3	NMT 50 CFU/4 hours
EU Grade D	NMT 200 CFU/meter^3	NMT 100 CFU/4 hours
Class 100/ISO 5	LT 0.1 CFU/foot^3	LT 1 CFU/4 hours
Class 10,000/ ISO 7	NMT 0.5 CFU/foot^3	NMT 5 CFU/4 hours
Class 100,000/ISO 8	NMT 2.5 CFU/foot^3	NMT 50 CFU/4 hours
A. No more than (NMT), less than (LT).		

Table D. Particles/viable environmental criteria.

Grade C rooms, with an approximate air exchange rate of 25 ACH. There was one Grade B room located within the Grade C suite. There are no AHUs that provide environmental control for Grade A areas; these environments are controlled through laminar flow hoods. Therefore, testing of Grade A areas were excluded in this case study as this area was still under control during the AHU shutdown. The two AHUs selected for the study are serviced by HEPA filters with a standard 99.97% efficiency rating at 0.3micron.

The AHUs selected for the study contained rooms representing various configurations: rooms adjacent to unclassified areas, rooms adjacent to lower grade air classifications, rooms considered high traffic areas, rooms where direct product processing occurs and rooms where no processing occurs. The test areas were in an idle state during study execution, whereby the areas were still considered GMP and under control, but no open or closed processing would occur during testing. At the onset of the AHU shutdown, all doors to unclassified and lower classification areas were opened and remained open throughout the shutdown period to simulate worst case reverse air flow. While opening the doors to the unclassified areas is not routine and would be considered a disruption to the controlled environment, there is the possibility that a door separating unclassified and classified areas could be inadvertently opened. When the adjacent unclassified areas maintain air pressure during a classified AHU shutdown, reverse air flow would occur from the unclassified area into the classified area. This is a worst case scenario. Personnel flowed throughout the testing area and simulated routine dynamic activities.

The AHUs were shut down for a duration of approximately three hours. At the end of the shutdown period, with the units still powered off, the shutdown samples were collected. Once the shutdown sampling was complete, the units were powered back on and all doors to the unclassified/adjacent areas were closed. The test areas were allowed to recover for approximately one hour, whereby the AHUs were in operation and limited personnel flow was allowed through the areas. No additional area cleaning was performed as part of the recovery. The second round of sampling, recovery sampling, was performed at the end of the one hour recovery period. There were 140 samples collected during each sample period: 62 air viable samples and 78 surface viable samples. The shutdown and recovery sample sets were duplicate sets of samples taken from different sites at the same relative sample location.

Sampling Methodology and Acceptance Criteria

Sample collection included surface viable sampling and active air viable sampling at routine environmental monitoring locations. The routine locations were identified as worst case locations during the initial facility cleaning validation. The study collected the same number of samples at each sampling period as during routine environmental monitoring. Passive air viable sampling could not be performed within the confines of the study because the AHU shutdown period (three hours) was not long enough to accommodate the continuous sampling period required for passive air viable sampling method <USP 1116>. Thus active air viable results represent dynamic air conditions for a greater air volume than passive air viable results, and as such, active air viable samples were collected at the routine passive air viable sampling locations. Non-viable sampling was not performed as viable sampling would represent worst case particulate and microorganism levels in the environment. Surface viable samples were taken using Tryptic Soy Agar (TSA) contact agar plates. Air viable samples were taken using an electric volumetric sampling device (100 L/min) at 1 m^3 with TSA media.

The viable limits were based on criteria outlined in environmental classifications per <USP1116> and EU cGMP Guidelines Annex 1 (2008), Table D. The acceptance criteria for the shutdown samples could not exceed the routine action limit while recovery samples could not exceed the routine alert limit. The shutdown acceptance criteria were intended to evaluate how much of an environmental disruption a temporary AHU shutdown would create, while the recovery acceptance criteria showed that the environment had returned to a controlled classified state. This case study itself was considered a planned environmental disruption; whereby any alert or action level results would be considered part of the disruption and addressed in the case study.

Results

All samples were submitted for growth determination (CFU/plate). All samples met their respective acceptance criteria. The results based on *growth* verses *no growth* were evaluated to determine the impact of the shutdown and the recovery periods. The overall percentage of shutdown and recovery samples with any microbial growth is shown in Figure 1.

The number of samples, both surface and dynamic air, exhibiting any level of growth was reduced significantly with the post recovery period. This comparison illustrates that

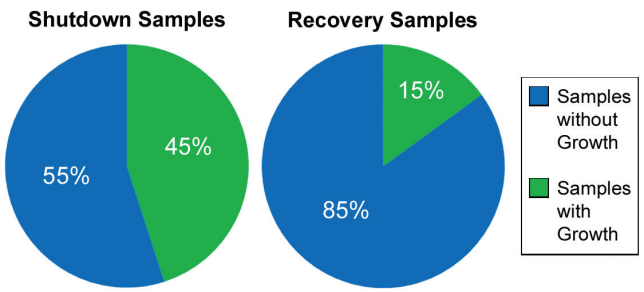

Figure 1. Samples with growth during shutdown and post recovery.

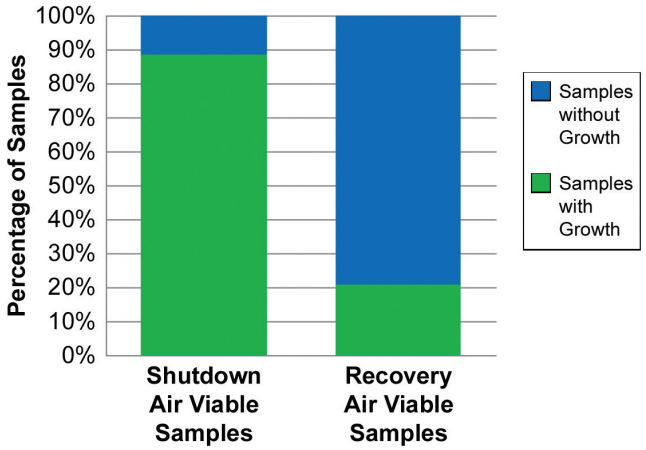

Figure 2. Air viable samples for shutdown and recovery samples.

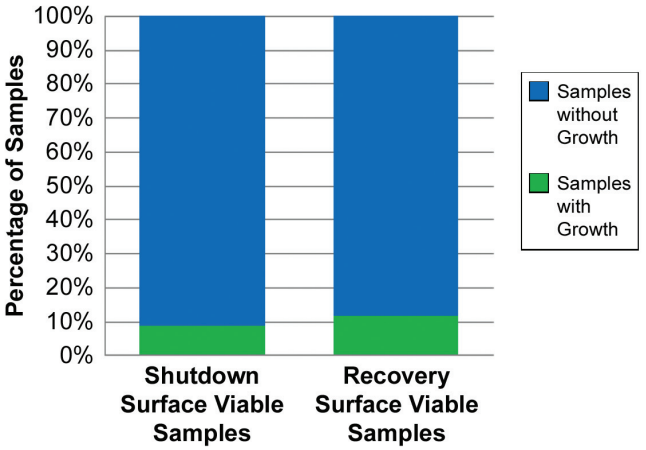

Figure 3. Surface viable samples for shutdown and recovery samples.

AHU operation alone decreases the overall number of microorganisms in the environment. For the recovery samples, the percentage of samples with growth (15%) was consistent with historical air viable and surface viable levels for the test areas. It also should be noted that all of the shutdown samples with growth were below the action levels of <10 CFU/m^3 for Grade B, <100 CFU/m^3 for Grade C, and <200 CFU/m^3 for Grade D.

An assessment of each type of sample, air viable and surface viable, also was performed. The percentage of air viable samples with growth by sample period is shown in Figure 2. The percentage of surface viable samples with growth by sample period is shown in Figure 3.

As shown in Figure 2, the number of air viable samples with microbial growth was significantly reduced from the shutdown sample period to the recovery sample period (89% to 21%). For the surface viable samples in Figure 3, growth during the shutdown and recovery sample periods was basically equivalent (9% and 12%). Surface viables would not be expected to increase during a temporary AHU shutdown at the same rate as air viable because air contaminants are more directly controlled by HEPA filtration. The recovery air viable and surface viable results support not performing additional area cleaning (surface cleaning) for a temporary AHU shutdown. In addition, the results further demonstrate that AHU operation, as a singular measure, decreases air viable levels below acceptance criteria for classified environments.

The samples with growth were further reviewed based on their relative location within the test area: adjacent to unclassified areas, high traffic areas, processing rooms, non-processing rooms, etc. The majority (89%) of shutdown air

Room Grade	Sample Description	Relative Location and Type				
		Adjacent to Unclassified	Adjacent to Lower Grade Level	High Traffic	Non-Processing	Processing
C	Surface Viables					X
D	Surface Viables	X		X	X	

Table E. Shutdown results and relative room location and type.

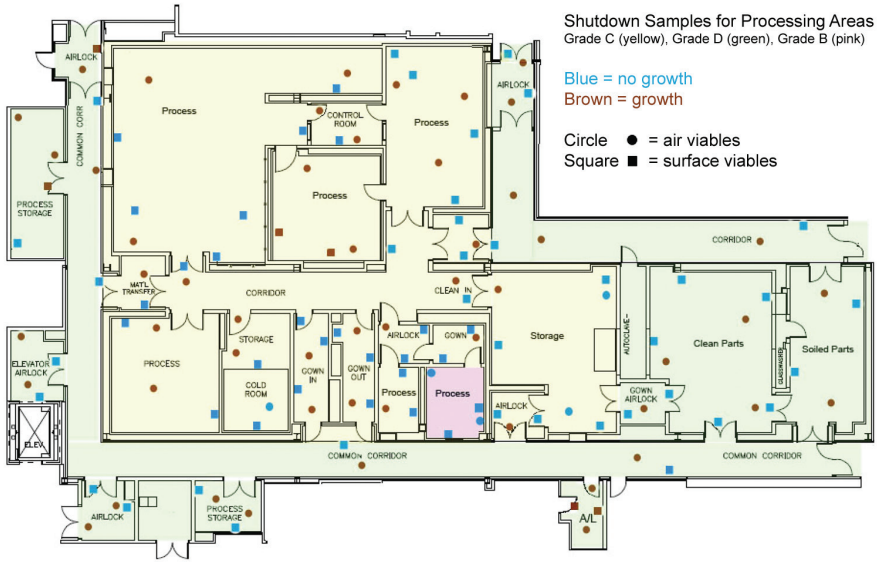

Figure 4. Location of shutdown samples and results.

viable results showed some level of viable growth; therefore, only shutdown surface viable samples were evaluated based on relative location within the test area. A summary of the shutdown results and relative room location are shown in Table E while detailed locations of each shutdown sample and result are shown in Figure 4.

The location of surface samples with growth showed a random distribution of samples with growth based on relative location and type. It was expected that room locations adjacent to unclassified areas or lower grade levels and rooms (or corridors) with higher traffic flows would have an increased potential for microbial growth. However, the shutdown surface results with growth occurred in both processing and non-processing rooms and were located throughout the test areas as opposed to being grouped in certain locations. Based on this comparison, no correlation was identified between room type or relative location and microbial growth during the shutdown sample period.

Both air and surface viable samples exhibiting growth were evaluated from the recovery sample period. The recovery results compared with the relative room locations and type are shown in Table F. Detailed locations for the recovery samples and results are shown in Figure 5.

Similarly, recovery samples with growth occurred mostly in non-processing rooms, but were located throughout both test areas including interior rooms, high traffic rooms and rooms that are adjacent to unclassified or lower grade level areas. The minimum volumetric turnover rate, room changes per minute (RCM), is >30 for Grade B and >20 for Grade C and D. Most GMP facilities operate with Grade C turnover rates between 27 to 28 RCM and Grade D turnover rates between 22 to 24 RCM in order to meet the recommended RCM rates. The lower RCM was speculated to cause the majority of the recovery samples with growth to be located in Grade D rooms. Based on this evaluation, there was no identified correlation between room type or relative location and microbial growth during the recovery sample period.

Room Grade	Sample Description	Relative Location and Type				
		Adjacent to Unclassified	Adjacent to Lower Grade Level	High Traffic	Non-Processing	Processing
C	Surface Viables				X	X
	Air Viables			X	X	X
D	Surface Viables	X		X	X	X
	Air Viables	X	X	X	X	

Table F. Recovery results and relative room location and type.

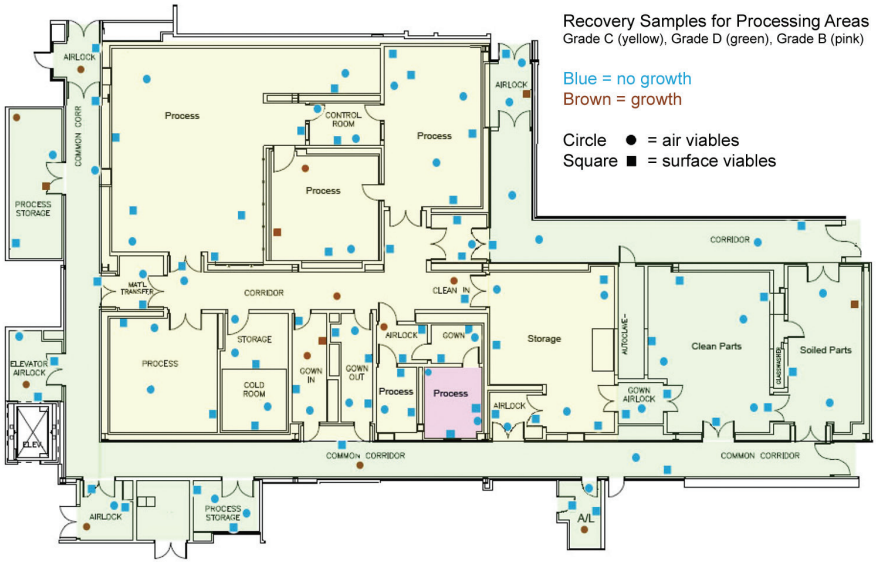

Figure 5. Location of recovery samples and results.

Conclusion

The environmental sampling results met all acceptance criteria for surface and air viable testing during the AHU shutdown sampling and recovery sampling events. These results demonstrated that environmental microbial levels increase during an AHU shutdown, and following an AHU recovery period of the classified environment, will return to acceptable environmental levels. Based on this study, it was recommended that a controlled GMP manufacturing environment would recover from a temporary AHU shutdown, whether planned or unplanned, of Not More Than (NMT) *three* hours by following the shutdown with Not Less Than (NLT) *two* hours of AHU operation; no additional area cleaning or environmental monitoring should be performed. A key aspect of this conclusion is that regardless of the type of shutdown, it is required that open processing should not occur during both the shutdown and recovery periods. If open processing occurs during any type of AHU shutdown, the routine required recovery response should be followed.

This case study demonstrated that when one key piece of environmental

control such as power to the AHU has been temporary lost, a full recovery to regain control within the environment can still be achieved without surface cleaning and environmental monitoring. When conditions permit, area surface cleaning may be eliminated when responding to an AHU shutdown, whether planned or unplanned. The data from this study does support that a recovery response that does not include area surface cleaning can return an area to its qualified state with minimal impact to the environment and product. The manufacturer should additionally perform a formal risk assessment prior to implementation to ensure all of the potential negative events are identified and mitigated to maintain product quality.

> *"...a standardized recovery that does not require physical cleaning and monitoring has the potential for meaningful savings.*

Cost Savings

The conclusions of the case study to evaluate a recovery period following AHU shutdowns with no additional area cleaning projected potential hard and soft cost savings. It was estimated that approximately 56 man hours and $2,500 in supplies could be saved per AHU annually by reducing cleaning and recovery operation costs associated with AHU shutdown and recovery. Savings include reduced or eliminated environmental monitoring and administrative efforts. Finally, resuming manufacturing operations in a timely manner without waiting for room cleaning and monitoring activities additionally benefits the manufacturing schedule. Considerable time and coordination goes into scheduling any maintenance activity, combined with additional time and coordination to release a classified area back into GMP production; therefore, a standardized recovery that does not require physical cleaning and monitoring has the potential for meaningful savings.

References

1. United States Pharmacopeia and National Formulary, USP <1116>--*Microbiological Evaluation of Cleanrooms and Controlled Environments*.

2. European Union (EU) GMP Annex 1, "Manufacture of Sterile Medicinal Products," 2008.

3. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 3 – Sterile Manufacturing Facilities,* International Society for Pharmaceutical Engineering (ISPE), First Edition, January 1999, www.ispe.org.

4. "Clean Rooms and Associated Controlled Environments, Part 1, Classification of Air Cleanliness," ISO 14644-1:1999(E), 1st ed., International Organization for Standardization, 1999.

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