Acceptability of Compressor-based Refrigeration in Cleanroom Environments

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1.0 BACKGROUND

1.1 Introduction

Cleanroom integrity is critical to pharmacy operations. Cleanrooms must adhere to strict guidelines to ensure the preservation of critical medications and safety of operators within the cleanroom environment. Facilities, personnel, procedures, and equipment must all meet pre-determined standards in order to maintain these strict conditions. United States Pharmacopeia (USP) standards for cleanroom validation are the guidance standards most used in pharmacy cleanroom settings today.

USP General Chapter <797> and General Chapter <800> represent two of the newest and most commonly adopted USP General Chapters related to cleanroom guidance in pharmacy settings. USP <797> is focused on sterile compounding practices and USP <800> is related to the compounding and storage of hazardous drugs. Both USP <797> and USP <800> cleanroom standards are based on International Organization for Standardization (ISO) Class 7 validated cleanroom requirements.

Cold storage is a necessary component for pharmacy cleanrooms, but there have been questions about the acceptability of certain refrigeration technology in validated cleanroom environments.

1.2 Compressor-Based Refrigeration vs. Thermo-electric Refrigeration

There are two primary methods of refrigeration used for medical-grade cold storage: compressor-based refrigeration and thermo-electric refrigeration. Compressor-based refrigeration uses a vapor-compression cycle – utilizing a compressor to rapidly heat refrigerant and force it through a series of coils. Refrigerant is then moved through an evaporator where rapid pressure release cools and partially evaporates the refrigerant which produces the effect of refrigeration.

Thermo-electric refrigeration uses the Peltier effect to maintain either hot or cold

temperatures. Thermo-electric refrigeration relies on p-type and n-type semiconductor materials forming a junction. When connected to a power source, electrons flow from one semiconductor type to another. Depending on the direction of this flow, thermo-electric refrigeration can produce a warming or cooling effect.

1.3 Concerns About Particulate Generation with Compressor-Based Refrigeration

Due to the moving parts involved in its operation, it has been hypothesized that compressor-based refrigeration may generate particles that may not be suitable for cleanroom environments. This test was conducted to determine whether or not compressor-based refrigeration is appropriate for these environments.

2.0 Testing Procedure

2.1 Purpose

Helmer Scientific contracted a third-party testing group to conduct a series of experiments on several Helmer refrigerator models designed for use in laboratory and pharmacy environments as well as a competitor refrigerator model. The purpose of the test is to determine the acceptability of a refrigerator to be used in an ISO Class 5 cleanroom; at rest; 0.5µm particle diameter. ISO Class 5 was chosen because it is two levels more stringent than the ISO Class 7 requirement outlined in USP <797> and USP <800>. Therefore, if a refrigerator is suitable for use in an ISO Class 5 environment, it will be suitable for use in an ISO Class 7 environment as well.

ISO Cleanroom Classification

ISO Class	Max Particles/m^3						Max Particles/ft^3	FS 209E Equivalent
	≥0.1µm	≥0.2µm	≥0.3µm	≥0.5µm	≥1.0µm	≥5.0µm	≥05µm	
Class 1	10							
Class 2	100	24	10					
Class 3	1,000	237	102	35			1	Class 1
Class 4	10,000	2,370	1,020	352	83		10	Class 10
Class 5	100,000	23,700	10,200	3,520	832	29	100	Class 100
Class 6	1,000,000	237,000	102,000	35,200	8,320	293	1,000	Class 1,000
Class 7				352,000	83,200	2,930	10,000	Class 10,000
Class 8				3,520,000	832,000	29,300	100,000	Class 100,000
Class 9				35,200,000	8,320,000	293,000		

2.2 Scope

The test protocol tested several Helmer refrigerator models, iPR113-GX, HLR105-GX, HPR120-GX, HLR125-GX and HPR226-GX as well as a competitor unit. The testing protocol was conducted at a third-party location and was intended to follow international standards ISO 14644 standard for cleanrooms and associated controlled environments Parts 1 and 14 except where otherwise specified.

3.0 Methodology

3.1 Setup and Control

A testing area was created to simulate an ISO 14644 Class 5 cleanroom environment. The area was divided into two sampling locations (Location 1A and 2A seen below). Two sampling locations is the minimum required number of sampling locations for a 4m2 environment per ISO 14644-1. The

spectrometer was placed in Location 1A, turned on, and the location was vacated to simulate an “at rest” environment. A sample equivalent to 1m3 of air was collected (sample length 59760s, 16hr 36 min) at a flow rate of 1L/min as suggested by ISO 14644-1:2015). The sample data was then exported, and the process was repeated for Location 2A.

Figure 1: Location 1A - top-down view

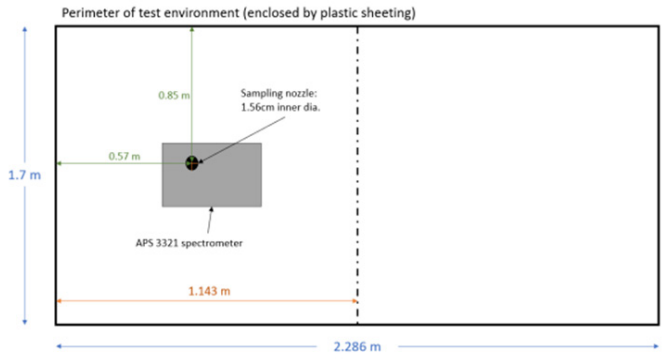
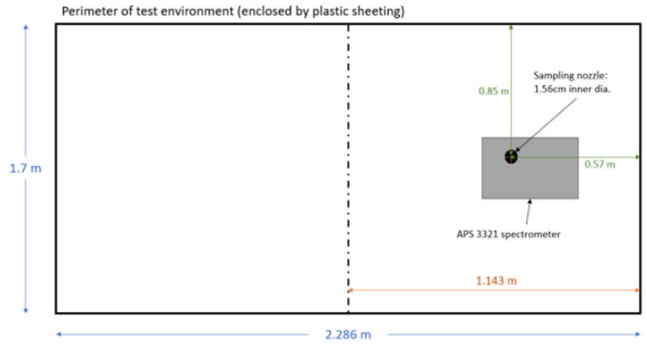


Figure 2: Location 2A - top-down view



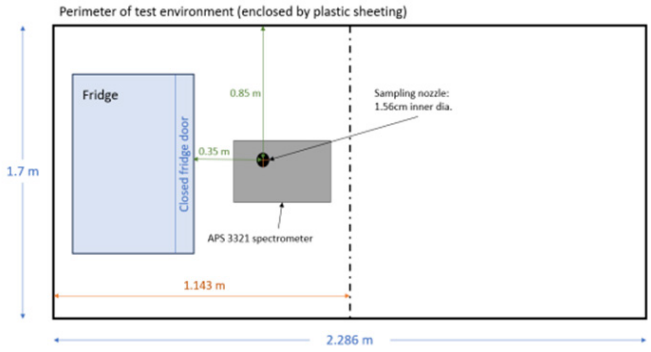
3.2 Testing

After the control samples were collected, a refrigerator was brought into the cleanroom simulation, unpackaged and visually inspected for particles, surface films, and inappropriately located lubricants such that the measurements to be taken would be unaffected. Results of the visual inspection were recorded to be compared with post-test inspection. The room temperature was set to 21.1°C (70°F) and relative humidity was set to 50%. Vertical airflow velocity was recorded using a thermos-anemometer and verified to be in range (between 0.3m/s and 0.5m/s according to ISO 14644-14).

The spectrometer was placed in Location 1B as depicted with roughly 2 inches between the back of the refrigerator and the plastic sheeting. The refrigerator door remained closed, and personnel evacuated the area during the test to simulate an “at rest” environment.

The refrigerator was powered on and allowed to come to preset internal temperature of 4°C. Upon reaching temperature, the room temperature and relative humidity were recorded again for the final test report.

Figure 3: Location 1B - top-down view



After internal temperature was reached, the room was vacated to simulate an “at rest” environment. Then a sampling protocol was used to collect appropriate air samples. Sample length was 600s (10min) and the

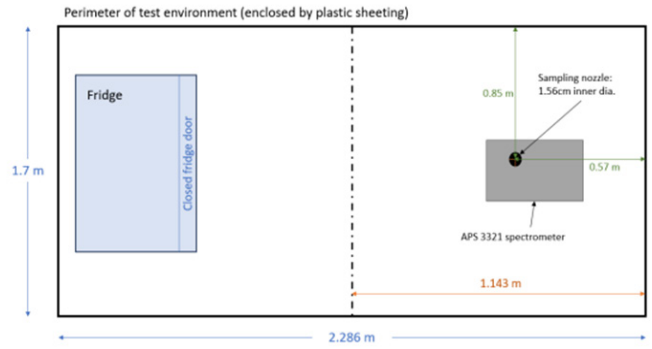
number of samples collected was 100. The ISO standard 14644-14 specifies a minimum sampling time of 1 minute and a minimum sampling volume of air of 2L for each sample, with a minimum of 100 samples taken in each sampling location for statistical analysis. Ten liters sampled over 10 minutes was chosen for this test to ensure that a total of 1m3 of air was tested.

Information was recorded and the number of total particles per 10L measurement were calculated along with standard deviation, 95% confidence interval, and z-value.

The spectrometer was then moved to the second cleanroom simulation area with no refrigerator (Location 2B) and the sample collection was repeated.

This testing process was repeated for each refrigerator model listed in Section 2.2.

Figure 4: Location 2B - top-down view



4.0 Results

4.1 Calculated Limits for ISO

Sampling volume was 10L for each sample (0.01m3). ISO 14644-1:2015 values were used to calculate class limit thresholds for ≥ 5µm particles. The target for this test was to achieve Class 5 status.

ISO Cleanroom Limits

ISO Class Number	Calculated Class Limit for ≥ 0.5µm (# of particles)
1	0
2	0
3	0.35
4	3.52
5	35.2
6	352
7	3,520
8	35,200
9	352,000

4.2 Statistical Results from 100 10L Air Samplings in Two Different Locations

The table below shows the statistical results of 100 samples of 10L each at two different locations (1B and 2B) at 1L/min flow rate.

Results

	Location 1B	Location 2B
Number of measured values, *n*	100	100
Mean value, N	0.65	0.34
Standard deviation, *s*	1.07	0.6
Maximum number of particles measured in a sample	8	3
Minimum number of particles measured in a sample	0	0
z-value for Class 5, ≥ 0.5µm diameter particles	320.87	575.82

Z-values for both locations exceed 1.645. According to ISO 14644-14:2016 this means

that the ISO Class 5 limit will not be exceeded with a confidence level of 95%.

5.0 Conclusions

5.1 Acceptability of Compressor-Based Refrigeration in ISO Class 5 Cleanroom Environment

The results of the test indicate that, according to ISO 14644-14:2016, the tested compressor-based refrigerator models have cleanroom suitability for use within a cleanroom of ISO Class 5 (≥ 0.5µm). The ISO Class 5 standards is two levels more stringent than the ISO Class 7 standard use to validate USP <797> and USP <800> cleanrooms.

5.2 Comparing Compressor-Based Refrigerators to Solid-State Thermoelectric Refrigerators

Test data indicates that under the conditions outlined in the test protocol, both compressor-based refrigerators and solid-state thermoelectric refrigerators may be suitable for use in ISO cleanroom environments. In fact, the test results from this study show that during testing, more particles were measured during testing for the 5.5 cubic-foot solid-state thermoelectric refrigerator (20) than during testing for the 25 cubic foot compressor-based refrigerator (17).

5.3 Other Considerations

Refrigeration configuration should also be considered when choosing refrigeration technology for cleanroom environments.

Pass-Thru Refrigerators - <USP> 797 allows the use of pass-thru cabinets, however it is a requirement that anteroom and cleanroom doors not be opened at the same time. USP recommends the use of interlock technology to prevent this occurrence. USP <800> does not allow the use of pass-thru cabinets.

Cleaning Protocols – It is important to review the acceptable cleaning agents that can be used on the refrigerators placed in your cleanroom environments. Equipment manufacturers should be able to provide test data on the acceptability of common cleansers on their equipment.

6.0 References

Full testing methodology and results on file at Helmer Scientific.

ISO 14644-1:2015 standard for cleanrooms and associated controlled environments Part 1: Classification of air cleanliness by particle concentration.

ISO 14644-14:2016 standard for cleanrooms and associated controlled environments Part 14: Assessment of suitability for use of equipment by airborne particle concentration.

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