

Pharmacy Isolator Performance Testing

The Baker Company Compounding Isolators and USP <797> Requirements

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ABSTRACT

The United States Pharmacopeia (USP) has recently released an In-Process Revision to Chapter <797> – Pharmaceutical Compounding – Sterile Preparations.¹ The Baker Company conducted a study to evaluate its pharmacy isolators using the criteria presented in the In-Process Revision. The results in this paper demonstrate that the SterilSHIELD (compounding aseptic isolator – CAI) and the ChemoSHIELD (compounding aseptic containment isolator – CACI) meet the performance criteria required by the In-Process Revision to USP Chapter <797> when located in an environment worse than ISO Class 7. ISO 5 conditions are maintained when the isolators are challenged with background conditions worse than ISO Class 9. Additionally, these requirements are met without the use of cleanroom garb.

1. INTRODUCTION

The first version of USP Chapter <797> became effective in January 2004 with publication in the first supplement to USP 27-NF 22 (as of this writing, this chapter is unchanged in the current USP 30-NF 25²). While requiring that preparation of compounded sterile products (CSPs) be done within an ISO Class 5 laminar air flow workstation (LAFW) located in an ISO Class 8 environment, the new chapter also introduced the alternative technology of barrier isolators. The language used to describe the acceptability of isolators was broad:²

“a well-designed positive pressure barrier isolator ...may offer an acceptable alternative to the use of conventional LAFWs in clean rooms for aseptic processing.”

This statement raised more questions than it answered. For instance, under what conditions is an isolator considered an *acceptable alternative*? Are negative pressure isolators (used for aseptic preparation of hazardous drugs) also acceptable? What constitutes *well-designed*? As iso-

lator technology was relatively new to the pharmacy setting, little experience and no standards existed for guidance in evaluating isolators for pharmacy compounding.

The community of pharmacists, equipment manufacturers, and equipment test professionals has since acted to fill this void. Most notably the Controlled Environment Testing Association (CETA) released an *Applications Guide for Compounding Isolators*³ (CAG 001-2005) providing information for the selection and use of compounding isolators, and a *Compounding Isolator Testing Guide*⁴ (CAG 002-2006) providing information on recommended performance tests for compounding isolators. These documents have become invaluable resources regarding the proper use and testing of compounding isolators.

In May of 2006, the USP expert committee on sterile compounding released the In-Process Revision to Chapter <797>.¹ While this document is not yet official, it provides a good indication of the future direction of this regulation. The proposed requirement for cleanrooms has been increased from ISO Class 8 to ISO Class 7 (this is an order of magnitude in terms of maximum allowed airborne particles, from 100,000 per cubic foot to 10,000 per cubic foot). (See Table 1 for a summary of air cleanliness classifications.)

ISO Class	Particles/m ³ (≥0.5 μm)	FS209E Class	Particles/ft ³ (≥0.5 μm)
Class 1	n/a	n/a	n/a
Class 2	4	n/a	n/a
Class 3	35	Class 1	1
Class 4	352	Class 10	10
Class 5	3,520	Class 100	100
Class 6	35,200	Class 1,000	1,000
Class 7	352,000	Class 10,000	10,000
Class 8	3,520,000	Class 100,000	100,000
Class 9	35,200,000	n/a	n/a

Table 1: Summary of Air Cleanliness Classifications
Adapted from ISO 14644-1, Classification of Air Cleanliness⁵

Additionally, the In-Process Revision¹ does provide some more objective performance expectations for a compounding aseptic isolator, or CAI (this term has replaced barrier isolator in the In-Process Revision). The section entitled “Placement of Primary Engineering Controls within ISO Class 7 Buffer Areas” states:

“The isolator must provide isolation from the room and maintain ISO Class 5 during dynamic operating conditions including transferring ingredients, components, and devices into and out of the isolator and during preparation of CSPs. Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site must maintain ISO Class 5 levels during compounding operations. It is incumbent on the compounding personnel to obtain documentation from the manufacturer that the CAI will meet this standard when located in worse than ISO Class 7 environments.”

The study described below will demonstrate that compounding isolators from The Baker Company exceed the performance criteria presented in the In-Process Revision to Chapter <797>. This study was performed by purposefully elevating the background particle count within a room, then performing tests adapted from the CETA Isolator Testing Guide, and measuring the particle counts within the isolator. Additional guidance for the study design is derived from provisions for aseptic processing set forth by the Food and Drug Administration (FDA)⁹ and the Parenteral Drug Association (PDA)⁸.

2. MATERIALS

This study was conducted within an air flow study laboratory, with a volume of approximately 4,000 cubic feet. The following materials and equipment were used in this study:

- SterilSHIELD, model SS500, Compounding Aseptic Isolator (CAI)
- ChemoSHIELD, model CS500, Compounding Aseptic Containment Isolator (CACI)
- Particle counter with isokinetic probe, Model A-2408, MetOne
- Aerosol Diluter, model 450AD, Milholland Associates
- Microspheres (polystyrene latex spheres), 0.26 μ m diameter, Milholland Associates
- Aerosol generator (modified humidifier), model HM486, Holmes
- Stainless steel transfer trays (1 solid, 1 perforated)
- 24" fan for mixing aerosol challenge with the room background

The aerosol generator was created by reducing the reservoir volume of a standard humidifier (See Figure 1). This was accomplished by attaching a small bottle over

the water inlet, secured with marine sealant. Varying levels of microsphere challenge were used (using the humidifier controls). A “high level” setting was used to generate the background challenge in the room, using the standard humidifier misting outlet. A “low level” setting was used to generate the cross-contamination challenge within the isolator, by attaching a 3-inch diameter hose to the misting outlet.



Figure 1: Microsphere Aerosol Generator

The elevated background of particles was achieved using microspheres (formerly called polystyrene latex, or PSL, spheres), in suspension with water, and aerosolized using a modified off the shelf humidifier. The advantage of microspheres is that they will not damage the optics of a particle counter, thus allowing you to measure extremely high airborne concentrations (with the use of an aerosol diluter, see Figure 2).

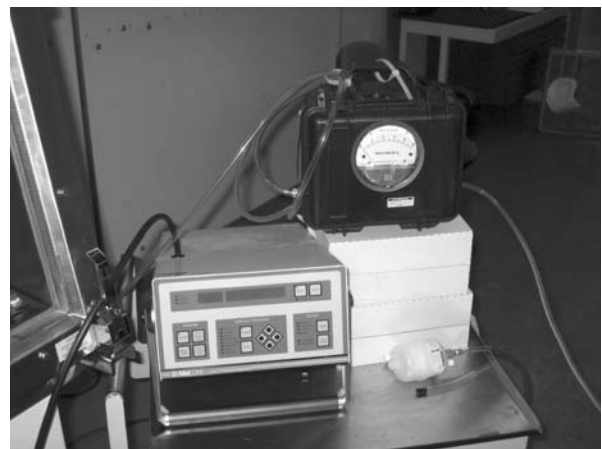


Figure 2: Particle Counter and Diluter

The microspheres used were 0.26 micrometer (μ m) in diameter, which produce particles of 0.3 μ m due to coating of microspheres with a layer of surfactant/water (as well as greater size particles from agglomeration of microspheres). Data were collected at 0.3 μ m and 0.5 μ m and greater (see the appendix for 0.3 μ m and greater results). The aerosol generator, with the settings used, produced a calculated 1.9×10^8 particles/minute of 0.5 μ m or greater

particles (see Table 2, below). The calculation assumes a 25% efficiency after accounting for evaporation, after experience with a collision nebulizer.^{6,7}

Background for each test, as reported below, was well in excess of ISO Class 9 (the ISO standard does not define a Class 10). We believe that this level of challenge was quite severe, representing at least 1-2 orders of magnitude greater than would be encountered in a pharmacy setting. As a point of reference, the CETA testing guide⁴ recommends a background challenge of at least 100,000 particles of 0.5µm or greater per cubic foot (the ISO Class 8 limit). This study was conducted at levels of 1.8-3.7 million particles of 0.5µm or greater per cubic foot in the surrounding environment.

3. METHODS AND RESULTS

A. Static (At-rest) Particle Level Test (CETA 2.10a) – Elevated Background Challenge

The purpose of this test was to demonstrate that the isolators could achieve and maintain ISO Class 5 under at-rest conditions while located in worse than ISO Class 7 ambient environment. The microsphere aerosol generator was run continuously to reach a background challenge of ISO 9+ (over 1 million particles of 0.5µm and greater per cubic foot).

Procedure

1. Place particle counter sample tube through sample port in isolator front view screen.
2. Place particle counter isokinetic probe in center of work surface, directly below IV bar and 6 inches above work surface.
3. Place aerosol diluter sample tube in the room ambient air (positioned approximately at operator height, in the center of the exterior of the isolator).
4. Determine that particle sampling tube has been appropriately purged of particles.
5. Perform the particle counter background noise count rate (zero count) test prior to sampling.
6. Turn on the microsphere aerosol generator to elevate the background; use highest setting possible.
7. The Compounding Isolator should be empty, clean, and safe for access when tested.
8. Switch the particle counter sampler tube to the isokinetic probe.
9. Sample the isolator work chamber for a period of 1 minute and record the particle level.
10. Switch the sample tube to the aerosol diluter.
11. Sample the ambient room air for a period of 1 minute and record the particle level.
12. Repeat steps 8-11 until the isolator work chamber fails to maintain ISO Class 5 levels, or until the maximum attainable background concentration is reached (whichever occurs first).

SterilSHIELD Results

Test Run	Background Challenge	ISO Class 5 Limit	Isolator Chamber Actual	Result
	(particles of 0.5µm and greater per cubic foot)			
1	1,168,650	100	0	PASS
2	1,254,204	100	0	PASS
3	1,228,626	100	0	PASS
4	1,330,056	100	0	PASS
5	1,315,944	100	1	PASS
6	1,314,621	100	0	PASS
7	1,362,690	100	0	PASS
8	1,391,796	100	0	PASS
9	1,424,871	100	0	PASS
10	1,610,532	100	0	PASS
11	1,768,851	100	0	PASS
12	1,902,915	100	0	PASS
13	2,144,583	100	0	PASS
14	2,349,648	100	1	PASS
15	2,593,521	100	0	PASS
16	3,033,639	100	0	PASS
17	3,228,561	100	0	PASS
18	3,311,028	100	0	PASS
19	3,464,937	100	0	PASS
20	3,613,995	100	0	PASS
21	3,778,047	100	0	PASS
22	3,775,842	100	0	PASS

ChemoSHIELD Results

Test Run	Background Challenge	ISO Class 5 Limit	Isolator Chamber Actual	Result
	(particles of 0.5µm and greater per cubic foot)			
1	241,280	100	0	PASS
2	242,672	100	0	PASS
3	291,392	100	0	PASS
4	346,144	100	0	PASS
5	434,304	100	1	PASS
6	492,304	100	0	PASS
7	478,384	100	0	PASS
8	547,520	100	0	PASS
9	561,440	100	0	PASS
10	617,120	100	0	PASS
11	709,920	100	0	PASS
12	698,320	100	0	PASS
13	792,976	100	0	PASS
14	946,096	100	1	PASS
15	1,024,512	100	0	PASS
16	1,050,032	100	0	PASS
17	1,054,208	100	0	PASS
18	1,158,608	100	0	PASS
19	1,617,040	100	0	PASS
20	1,601,264	100	0	PASS
21	1,883,840	100	0	PASS
22	1,878,272	100	0	PASS
23	1,975,712	100	0	PASS

For the SterilSHIELD tests, background was gradually elevated until the maximum attainable particle counts were achieved. The background concentration was in excess of 3.7 million particles of 0.5µm and greater per cubic foot (ISO 9 limit is 1 million per cubic foot, ISO 8 is 100,000 per cubic foot).



Figure 3: ChemoSHIELD with background challenge sample tube

In the ChemoSHIELD test, background was again elevated. Note that the final background challenge achieved was lower with the ChemoSHIELD isolator. This is because the ChemoSHIELD isolator has filtered exhaust air, taking 100% of the isolator airflow out through the building exhaust, which is then replaced with filtered supply air. This effectively dilutes (or cleans) the room air to a much greater extent than does the SterilSHIELD (which exchanges a smaller volume of filtered air with the room).

Both isolators demonstrated the ability to maintain ISO Class 5 conditions within the work chamber under at-rest conditions when located in an ISO 9+ area. Neither isolator departed from ISO 5, even at the maximum attainable background concentration.

B. PREPARATION INGRESS AND EGRESS TEST (CETA 2.09) – ELEVATED BACKGROUND CHALLENGE

The purpose of this test was to demonstrate that the isolators could maintain ISO Class 5 conditions during the transfer of materials into and out of the work chamber via the integral transfer chamber, when located in worse than an ISO Class 7 ambient environment. This follows from the PDA Technical Report on isolators⁸ which calls for “defined openings that have been designed and validated to preclude the transfer of contamination.” The generator was run continually to elevate background contamination to an ISO 9+ level.

For both isolator models, test runs were performed with both inbound and outbound materials, utilizing two different stainless steel transfer trays (one solid, one perforat-

ed). For the SterilSHIELD, additional test runs were performed leaving both outer and inner pass through doors open to simulate a failure condition. For the ChemoSHIELD, pass-through purge times were varied between zero and 30 seconds.

Procedure

1. Place particle counter sample tube through sample port in isolator front view screen.
2. Place aerosol diluter sample tube in the room ambient air (positioned approximately at operator height, in the center of the exterior of the isolator).
3. Place the particle counter probe in the Main Chamber, 6 inches above the isolator work surface. SterilSHIELD: locate 2 inches inside the inner pass-through chamber door, even with the front edge of the door. ChemoSHIELD: locate 2 inches inside the path of the swinging inner pass-through chamber door, centered back to front on the work surface. Probe placement should be so that the operator’s arms will not pass directly over the probe when removing material from the pass-through.
4. Turn on the microsphere aerosol generator to elevate the background; use highest setting possible.
5. Measure room background particle level.
6. Verify the isolator chamber particle counts meet ISO Class 5 levels before beginning the test cycle.
7. Set the particle counter for a one minute count with no more than a one second hold time.
8. Open the outside pass-through door.
9. Place an empty transfer tray into the pass-through and close the outer door.
10. Wait for the pass-through purge cycle time (SterilSHIELD requires no wait time; ChemoSHIELD time varied through the test from zero up to 30 seconds).
11. Open the inside pass-through door and move the transfer tray from the pass-through to the work area.
12. Close the inside pass-through door.
13. Document the particle counts for a period of one minute, including the transfer process.
14. Repeat steps 8-13, reversing the direction to move materials out of the isolator.
15. Document the room background particle level.
16. SterilSHIELD only: Repeat steps 8-13, leaving the outside and inside pass through doors open throughout the transfer process.
17. Document the room background particle level.

SterilSHIELD Results

Test Run	Test Conditions (TRAY, IN, OUT, BOTH OPEN)	Background Challenge	ISO Class 5 Limit	Isolator Chamber Actual	Result
		(particles of 0.5µm and greater per cubic foot)			
	[start]	3,775,842			
1	Perforated tray, ingress		100	0	PASS
2	Perforated tray, egress		100	0	PASS
3	Solid tray, ingress		100	0	PASS
4	Solid tray, egress		100	3	PASS
5	Solid tray, ingress		100	2	PASS
6	Solid tray, egress		100	0	PASS
7	Perforated tray, ingress		100	9	PASS
8	Perforated tray, egress		100	0	PASS
	[background check]	3,807,153			
9	Perforated tray, both open [1]		100	8	PASS
	[background check]	4,011,177			
10	Solid tray, both open [1]		100	3	PASS
11	Solid tray, both open [1]		100	1	PASS
12	Solid tray, both open [1] [2]		100	11	PASS
	[background check]	3,788,631			
	[end]	4,079,250			

[1] Both outer and inner door opened, ingress and egress in one cycle, to simulate failure condition.

[2] Tray moved rapidly in and out of unit.

ChemoSHIELD Results

Test Run	Test Conditions (TRAY, IN, OUT, WAIT TIME)	Background Challenge	ISO Class 5 Limit	Isolator Chamber Actual	Result
		(particles of 0.5µm and greater per cubic foot)			
	[background check]	2,024,741			
1	Perforated tray, ingress, 0 seconds		100	17	PASS
2	Perforated tray, egress, 0 seconds		100	0	PASS
3	Perforated tray, ingress, 0 seconds		100	4	PASS
4	Perforated tray, egress, 0 seconds		100	73	PASS
5	Solid tray, ingress, 0 seconds		100	2	PASS
6	Solid tray, egress, 0 seconds		100	11	PASS
7	Solid tray, ingress, 0 seconds		100	0	PASS
8	Solid tray, egress, 0 seconds		100	1	PASS
	[background check]	2,009,584			
9	Solid tray, ingress, 23 seconds		100	3	PASS
10	Solid tray, egress, 23 seconds		100	13	PASS
11	Solid tray, ingress, 23 seconds		100	19	PASS
12	Solid tray, egress, 23 seconds		100	0	PASS
13	Solid tray, ingress, 23 seconds		100	15	PASS
14	Solid tray, egress, 23 seconds		100	0	PASS
	[background check]	1,948,336			
15	Perforated tray, ingress, 15 seconds		100	26	PASS
16	Perforated tray, egress, 15 seconds		100	4	PASS
17	Perforated tray, ingress, 15 seconds		100	203	FAIL
18	Perforated tray, egress, 15 seconds		100	5	PASS
19	Perforated tray, ingress, 15 seconds		100	0	PASS
20	Perforated tray, egress, 15 seconds		100	43	PASS
	[background check]	1,892,347			

Both units maintained ISO Class 5 conditions during ingress and egress of materials, while located in an environment of worse than ISO 9.

For the SterilSHIELD, no wait time is necessary before moving materials into the work chamber. The laminar flow design and the positive pressure operation allow the isolator to maintain ISO 5 conditions even when put into failure mode (leaving both inner and outer door fully open, with “rapid” material transfer).

For the ChemoSHIELD, a short wait time is required to purge the pass-through chamber of particles brought in by the negative pressure of the unit when the outer door is open. One failure was noted with a 15 second wait time. ISO 5 was maintained with a wait time of 23 seconds; a 1 minute wait time is recommended in the field to assure an extra margin of safety.



Figure 4: Particle counter sample probe (shown for ChemoSHIELD ingress/egress test)



Figure 5: Transfer tray for ingress/egress test

C. DYNAMIC OPERATING TEST (CETA 2.10B) – ELEVATED INTERNAL CHALLENGE

The purpose of this test was to show maintenance of ISO 5 conditions during compounding operations, including significant process generated contamination.

The test was performed while simulating compounding operations that may generate aerosols and disturb airflow patterns with arm and hand movement. This follows from FDA guidance⁹ that an aseptic system should “...maintain unidirectional airflow and air quality under dynamic conditions within the critical area.”

Additionally, the aerosol generator was run inside the isolator, downstream of the critical exposure site, to simulate excessive process generated contamination. The generated challenge was measured at 2.39×10^7 particles of $0.5\mu\text{m}$ and greater per cubic foot, with a calculated generation rate of at least 1.9×10^8 particles of $0.5\mu\text{m}$ or greater per minute (see Table 2). These differ because the generated microspheres are diluted when released into the clean downflow air of the isolator.

1.66×10^{13} particles @ $0.3\mu\text{m}$ /ml of stock suspension x 1.6 ml of stock = 2.56×10^{13} particles @ $0.3\mu\text{m}$ /ml $(2.56 \times 10^{13}$ particles @ $0.3\mu\text{m}$ /ml) / $(946$ ml/1 qt dilution) = 2.8×10^{10} particles @ $0.3\mu\text{m}$ /ml 2.8×10^{10} particles @ $0.3\mu\text{m}$ /ml x 2 ml/min (measured output of generator) = 5.6×10^{10} particles @ $0.3\mu\text{m}$ /min 5.6×10^{10} particles @ $0.3\mu\text{m}$ x 0.25 (estimated generator efficiency) = 1.4×10^9 particles @ $0.3\mu\text{m}$ /minute 1.4×10^9 particles @ $0.3\mu\text{m}$ /minute x 0.14 (measured ratio of $0.5\mu\text{m}$ to $0.3\mu\text{m}$ particles) = 1.9×10^8 particles @ $0.5\mu\text{m}$ and greater / minute

Table 2: Calculation of aerosol generation rate

Procedure

1. Place particle counter sample tube through sample port in isolator front view screen.
2. Place particle counter isokinetic probe within the airflow in center of work surface. Vertical position chosen where there is most expected risk to the exposed sterile preparation, in the critical area halfway between the IV bar and the work surface (approx. 11 inches from each).
3. Place the microsphere aerosol generator within the isolator, with the outlet located downstream of the particle counter probe, approximately 4 inches off of the work surface.
4. Determine that particle sampling tube has been appropriately purged of particles.
5. Perform the particle counter background noise count rate (zero count) test prior to sampling.

6. Compounding Isolator should contain all the cleaned surrogate compounding components that would support surrogate manipulation operation during the test.
7. Turn on the microsphere aerosol generator to the lowest setting.
8. To simulate actual preparation, perform surrogate manipulation using both gloves during particle testing to determine whether activity affects particle levels at the sample point.
9. Transfer 5ml of sterile water into a hanging bag of 0.9% sodium chloride during each 1 minute cycle.
10. Document the particle levels through each 1 minute cycle.

SterilSHIELD Results

Test Run	Aerosol Challenge	ISO Class 5 Limit	Critical Site Actual	Result
	(particles of 0.5µm and greater per cubic foot)			
1	> 23,000,000	100	0	PASS
2	> 23,000,000	100	0	PASS
3	> 23,000,000	100	0	PASS
4	> 23,000,000	100	0	PASS
5	> 23,000,000	100	0	PASS

ChemoSHIELD Results

Test Run	Aerosol Challenge	ISO Class 5 Limit	Critical Site Actual	Result
	(particles of 0.5µm and greater per cubic foot)			
1	> 23,000,000	100	0	PASS
2	> 23,000,000	100	0	PASS
3	> 23,000,000	100	0	PASS
4	> 23,000,000	100	0	PASS
5	> 23,000,000	100	0	PASS

Both isolators maintained ISO 5 conditions throughout simulated compounding activities, even with a particle challenge generated within the work zone. Generated particles are swept away by unidirectional (“laminar”) air flow and do not migrate back into the critical work zone.

D. CROSS-CONTAMINATION TEST – ELEVATED INTERNAL CHALLENGE

The purpose of this test is to show that process generated contamination does not re-enter the critical work zone. The procedure used for the Dynamic Operating Test was adapted to test for cross contamination within the isolator work chamber. The generated challenge was measured at 2.39×10^7 particles of 0.5µm and greater per cubic foot, with a calculated generation rate of 1.9×10^8 particles of 0.5µm or greater per minute.



Figure 6: Microsphere aerosol for dynamic and cross-contamination test



Figure 7: Dynamic Operating Test setup

Procedure

The aerosol generator was placed on the left and then the right sidewall of the isolator work chamber to test for cross-contamination within the chamber. The challenge outlet hose was approximately 4 inches from the sidewall (first right side, then repeated on left side), centered (back to front) below the unit’s IV bar (*see Figure 8*). The particle counter probe was located 11 inches above the work surface, and 11 inches below the IV bar, with a series of one minute samples taken.

1. Place particle counter sample tube through sample port in isolator front view screen.
2. Place particle counter isokinetic probe within the air flow in center of work surface. Vertical position chosen where there is most expected risk to the exposed sterile preparation, in the critical area halfway between the IV bar and the work surface (approximately 11 inches from each).
3. Place the microsphere aerosol generator within the isolator, positioned 4 inches from the right sidewall,

and directly below the IV bar, with the generator outlet hose approximately 4 inches above the work surface.

4. Determine that particle sampling tube has been appropriately purged of particles.
5. Perform the particle counter background noise count rate (zero count) test prior to sampling.
6. Compounding Isolator should contain all the cleaned surrogate compounding components that would support surrogate manipulation operation during the test.
7. Turn on the microsphere aerosol generator to the lowest setting.
8. To simulate actual preparation, perform surrogate manipulation using both gloves during particle testing to determine whether activity affects particle levels at the sample point.
9. Transfer 5ml of sterile water into a hanging bag of 0.9% sodium chloride during each 1 minute cycle.
10. Document the particle levels for a 1 minute cycle.
11. Repeat with microsphere aerosol generator on left side of isolator work chamber, 4 inches from the side-wall and directly below the IV bar.

SterilSHIELD Results

Right Side

Test Run	Aerosol Challenge	ISO Class 5 Limit	Critical Site Actual	Result
	(particles of 0.5µm and greater per cubic foot)			
1	> 23,000,000	100	0	PASS
2	> 23,000,000	100	0	PASS
3	> 23,000,000	100	0	PASS

Left Side

Test Run	Aerosol Challenge	ISO Class 5 Limit	Critical Site Actual	Result
	(particles of 0.5µm and greater per cubic foot)			
1	> 23,000,000	100	0	PASS
2	> 23,000,000	100	0	PASS
3	> 23,000,000	100	0	PASS

ChemoSHIELD Results

Right Side

Test Run	Aerosol Challenge	ISO Class 5 Limit	Critical Site Actual	Result
	(particles of 0.5µm and greater per cubic foot)			
1	> 23,000,000	100	0	PASS
2	> 23,000,000	100	0	PASS
3	> 23,000,000	100	0	PASS
4	> 23,000,000	100	0	PASS
5	> 23,000,000	100	0	PASS

Left Side

Test Run	Aerosol Challenge	ISO Class 5 Limit	Critical Site Actual	Result
	(particles of 0.5µm and greater per cubic foot)			
1	> 23,000,000	100	0	PASS
2	> 23,000,000	100	0	PASS
3	> 23,000,000	100	0	PASS
4	> 23,000,000	100	0	PASS
5	> 23,000,000	100	0	PASS

One issue was encountered with the test setup for the ChemoSHIELD cross-contamination challenge. The aerosol generator itself is relatively large (18" wide x 6" deep x 20" high) compared to the work chamber of the ChemoSHIELD model CS500 (measuring 31" wide x 24" deep x 25" high). To maintain unidirectional airflow, it was necessary to carefully place the aerosol generator so as not to block the return air slots in the work surface during the left side cross-contamination challenge. This underscores the importance of properly arranging equipment and supplies within the work area.

Both isolators maintained ISO Class 5 conditions throughout the cross-contamination challenge test.

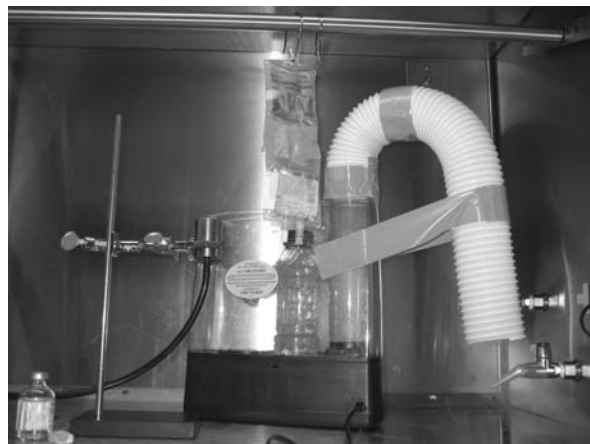


Figure 8: Cross-Contamination Test setup

4. CONCLUSIONS

The test results presented in this paper demonstrate that the SterilSHIELD compounding aseptic isolator and the ChemoSHIELD compounding aseptic containment isolator, when properly used and maintained, are able to maintain ISO 5 conditions, under dynamic operating conditions, while located in worse than an ISO 7 environment.

The background particle levels used in this study were at levels exceeding ISO Class 9, orders of magnitude beyond what would be expected in a pharmacy setting, and ISO 5 was maintained through the transfer of materials and during simulated compounding activities (as well as selected failure conditions).

Note that no cleanroom garb or personal protective equipment (PPE) was worn by laboratory personnel during these tests (other than the isolator gloves themselves, and respirators for protection from the experimental challenge when the room background was elevated). Also, no surface wipe down (i.e., alcohol or other sanitization) was performed on the interior of the isolators or on materials brought into and out of the isolators.

The effect of garb or PPE and surface wipe downs on aseptic conditions still must be accounted for, particularly as they relate to surface contamination (which is not measured by a particle counter). When handling hazardous drugs, careful cleaning and PPE are important to minimize the risk of personnel exposure. Each facility

should have appropriate standard operating procedures (SOPs) for material handling and use of PPE to avoid surface contamination (aseptic conditions) and personnel exposure (hazardous drugs).

In summary, both the SterilSHIELD CAI and the ChemoSHIELD CACI maintain ISO Class 5 conditions within the work area when located in worse than an ISO Class 7 environment, as required by the In-Process Revision to USP Chapter <797> and tested according to CETA CAG 002-2006. ISO Class 5 is maintained during the ingress and egress of materials, during simulated compounding activities, and when subjected to a simulated process-generated cross-contamination challenge.

REFERENCES

1. United States Pharmacopeia; *In-Process Revision: <797> Pharmaceutical Compounding – Sterile Preparations*; Pharmacopeial Forum 32(3), May-June 2006.
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APPENDIX A: 0.3µm AND GREATER RESULTS

1. Static (At-rest) Particle Level Test (CETA 2.10a) – Elevated Background Challenge

SterilSHIELD Results

Test Run	Background Challenge	ISO Class 5 Limit	Isolator Chamber Actual	Result
	(particles of 0.3µm and greater per cubic foot)			
1	9,293,193	288	1	PASS
2	9,610,713	288	0	PASS
3	9,563,526	288	4	PASS
4	9,880,164	288	1	PASS
5	9,778,293	288	3	PASS
6	10,325,574	288	3	PASS
7	10,706,598	288	2	PASS
8	10,945,179	288	4	PASS
9	10,959,732	288	4	PASS
10	11,809,098	288	3	PASS
11	12,660,228	288	5	PASS
12	13,655,124	288	3	PASS
13	14,892,129	288	11	PASS
14	16,050,195	288	4	PASS
15	17,592,372	288	4	PASS
16	19,344,906	288	3	PASS
17	20,555,892	288	3	PASS
18	21,791,574	288	5	PASS
19	22,367,961	288	8	PASS
20	23,520,735	288	4	PASS
21	24,142,104	288	3	PASS
22	24,259,851	288	2	PASS

ChemoSHIELD Results

Test Run	Background Challenge	ISO Class 5 Limit	Isolator Chamber Actual	Result
	(particles of 0.3µm and greater per cubic foot)			
1	1,590,538	288	0	PASS
2	2,115,376	288	0	PASS
3	2,490,288	288	1	PASS
4	2,851,280	288	1	PASS
5	3,208,560	288	2	PASS
6	3,744,016	288	1	PASS
7	4,022,416	288	0	PASS
8	4,186,672	288	155	PASS
9	4,527,712	288	0	PASS
10	4,539,776	288	4	PASS
11	4,940,672	288	5	PASS
12	5,339,712	288	0	PASS
13	5,508,608	288	0	PASS
14	5,748,960	288	2	PASS
15	6,676,960	288	0	PASS
16	7,003,152	288	3	PASS
17	7,235,152	288	2	PASS
18	7,347,904	288	1	PASS
19	7,870,368	288	0	PASS
20	11,109,552	288	0	PASS
21	11,535,504	288	0	PASS
22	12,834,704	288	0	PASS
23	12,891,776	288	3	PASS

2. Preparation Ingress and Egress Test (CETA 2.09) – Elevated Background Challenge

SterilSHIELD Results

Test Run	Test Conditions (TRAY, IN, OUT, BOTH OPEN)	Background Challenge	ISO Class 5 Limit	Isolator Chamber Actual	Result
		(particles of 0.3µm and greater per cubic foot)			
	[start]	24,259,851			
1	Perforated tray, ingress		288	10	PASS
2	Perforated tray, egress		288	4	PASS
3	Solid tray, ingress		288	7	PASS
4	Solid tray, egress		288	10	PASS
5	Solid tray, ingress		288	8	PASS
6	Solid tray, egress		288	7	PASS
7	Perforated tray, ingress		288	23	PASS
8	Perforated tray, egress		288	9	PASS
	[background check]	23,441,687			
9	Perforated tray, both open [1]		288	17	PASS
	[background check]	25,080,993			
10	Solid tray, both open [1]		288	17	PASS
11	Solid tray, both open [1]		288	15	PASS
12	Solid tray, both open [1] [2]		288	46	PASS
	[background check]	24,926,222			
	[end]	25,244,604			

[1] Both outer and inner door opened, ingress and egress in one cycle, to simulate failure condition.

[2] Tray moved rapidly in and out of unit.

Test Run	Test Conditions (TRAY, IN, OUT, WAIT TIME)	Background Challenge	ISO Class 5 Limit	Isolator Chamber Actual	Result
		(particles of 0.3µm and greater per cubic foot)			
	[background check]	13,672,224			
1	Perforated tray, ingress, 0 seconds		288	67	PASS
2	Perforated tray, egress, 0 seconds		288	6	PASS
3	Perforated tray, ingress, 0 seconds		288	39	PASS
4	Perforated tray, egress, 0 seconds		288	175	PASS
5	Solid tray, ingress, 0 seconds		288	36	PASS
6	Solid tray, egress, 0 seconds		288	92	PASS
7	Solid tray, ingress, 0 seconds		288	4	PASS
8	Solid tray, egress, 0 seconds		288	4	PASS
	[background check]	13,518,485			
9	Solid tray, ingress, 23 seconds		288	23	PASS
10	Solid tray, egress, 23 seconds		288	41	PASS
11	Solid tray, ingress, 23 seconds		288	108	PASS
12	Solid tray, egress, 23 seconds		288	3	PASS
13	Solid tray, ingress, 23 seconds		288	124	PASS
14	Solid tray, egress, 23 seconds		288	0	PASS
	[background check]	13,304,581			
15	Perforated tray, ingress, 15 seconds		288	196	PASS
16	Perforated tray, egress, 15 seconds		288	5	PASS
17	Perforated tray, ingress, 15 seconds		288	680	FAIL
18	Perforated tray, egress, 15 seconds		288	18	PASS
19	Perforated tray, ingress, 15 seconds		288	4	PASS
20	Perforated tray, egress, 15 seconds		288	129	PASS
	[background check]	13,009,168			

3. Dynamic Operating Test (CETA 2.10b) – Elevated Internal Challenge

SterilSHIELD Results

Test Run	Aerosol Challenge	ISO Class 5 Limit	Critical Site Actual	Result
	(particles of 0.3µm and greater per cubic foot)			
1	> 23,000,000	288	4	PASS
2	> 23,000,000	288	1	PASS
3	> 23,000,000	288	0	PASS
4	> 23,000,000	288	2	PASS
5	> 23,000,000	288	1	PASS

ChemoSHIELD Results

Test Run	Aerosol Challenge	ISO Class 5 Limit	Critical Site Actual	Result
	(particles of 0.3µm and greater per cubic foot)			
1	> 234,000,000	288	0	PASS
2	> 234,000,000	288	0	PASS
3	> 234,000,000	288	0	PASS
4	> 234,000,000	288	2	PASS
5	> 234,000,000	288	0	PASS

4. Cross Contamination Test – Elevated Internal Challenge

SterilSHIELD Results

Right Side

Test Run	Aerosol Challenge	ISO Class 5 Limit	Critical Site Actual	Result
	(particles of 0.3µm and greater per cubic foot)			
1	> 234,000,000	288	2	PASS
2	> 234,000,000	288	4	PASS
3	> 234,000,000	288	3	PASS

Left Side

Test Run	Aerosol Challenge	ISO Class 5 Limit	Critical Site Actual	Result
	(particles of 0.3µm and greater per cubic foot)			
1	> 234,000,000	288	2	PASS
2	> 234,000,000	288	2	PASS
3	> 234,000,000	288	1	PASS

ChemoSHIELD Results

Right Side

Test Run	Aerosol Challenge	ISO Class 5 Limit	Critical Site Actual	Result
	(particles of 0.3µm and greater per cubic foot)			
1	> 234,000,000	288	1	PASS
2	> 234,000,000	288	0	PASS
3	> 234,000,000	288	2	PASS
4	> 234,000,000	288	1	PASS
5	> 234,000,000	288	0	PASS

Left Side

Test Run	Aerosol Challenge	ISO Class 5 Limit	Critical Site Actual	Result
	(particles of 0.3µm and greater per cubic foot)			
1	> 234,000,000	288	12	PASS
2	> 234,000,000	288	8	PASS
3	> 234,000,000	288	113	PASS
4	> 234,000,000	288	6	PASS
5	> 234,000,000	288	0	PASS

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