PRACTICE REPORT

Generation of particulate matter during handling of needle and syringe packaging

ERIC S. KASTANGO, JAMES T. WAGNER, KARI B. KASTANGO, NICHOLAS E. KASTANGO, AND TERRY J. WAGNER

Purpose. Generation of airborne particulate matter during the handling and opening of various syringe and needle packages in a laminar-airflow workbench (LAFW) and in a biological safety cabinet (BSC) was measured to compare the effects on air cleanliness conditions (International Organization for Standardization [ISO] class 5 within the LAFW or BSC and ISO class 7 in buffer areas).

Methods. Twenty-five to 50 packages of each of 12 needle or syringe products were opened. Probes were configured to count airborne particles during the separation of strip packages and the opening of packages by peeling back the top web or pushing the device through the packaging (for soft packages) or by twisting apart hard packages.

Results. The numbers of particles were not significantly different between the LAFW and BSC. The separation of strip packages generated visible particles and raised airborne particle counts. Peeling open plastic film packages and opening hard plastic packages generated fewer airborne particulates than did pushing devices through the packaging. For all methods of package opening, average counts downstream from the direct compounding area exceeded ISO class 5 conditions. Counts in the LAFW buffer area did not exceed ISO class 7.

Conclusion. All methods of separating and opening the packaging of needles and syringes generated particles. The peel-and-present technique generated the lowest particulate volume. The LAFW and BSC were equally effective in maintaining low particle counts.

Index terms: Air; Contamination; Control, quality; Equipment; Needles; Packaging; Syringes

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Recently, Trissel et al.[1] demonstrated that the use of proper aseptic work practices by pharmacists and technicians can have a favorable effect on the rate of contamination of compounded sterile preparations (CSPs). These practices include wiping down components before placing them in the primary engineering control (i.e., laminar-airflow workbench [LAFW] or biological safety cabinet [BSC]) and routinely disinfecting gloved hands with wipes or pads wetted with 70% isopropyl alcohol.

Almost 30% of respondents to a recent survey of the impact of *United States Pharmacopeia* (*USP*) chapter 797 reported that they do not wipe down components and equipment prior to placement in the buffer area, even though chapter 797 mandates this practice.[2] Chapter 797 contains critically important minimum practice and quality standards intended to prevent patient harm, including death, as a result of (1) microbial contamination (nonsterility), (2) excessive bacterial endotoxins, (3) variability in the intended strength of correct ingredients that exceeds either monograph limits for official articles or 10% for nonofficial articles, (4) unintended chemical and physical contaminants, or (5) ingredients of inappropriate quality in CSPs.[3]

We conducted a study to examine and reinforce the aseptic compounding principles underlying chapter

ERIC S. KASTANGO, M.B.A., B.S.PHARM., FASHP, is President, Clinical IQ, LLC, Florham Park, NJ. JAMES T. WAGNER is President, Controlled Environment Consulting, Hellertown, PA. KARI B. KASTANGO, M.S., PH.D., is Senior Biostatistician, Averion International Corp., Southborough, MA. NICHOLAS E. KASTANGO is pursuing a B.S. degree in integrated business and engineering, Lehigh University, Bethlehem, PA. TERRY J. WAGNER is pursuing a B.S. degree in food sciences, Penn State University, College Station, PA.

Address correspondence to Eric S. Kastango at Clinical IQ, LLC, 184 Columbia Turnpike, Suite 282, Florham Park, NJ 07932-1314 (eric.kastango@clinicaliq.com).

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797. Our study had three objectives: (1) to statistically determine if the number of particles generated during the opening of packages is different between two types of primary engineering controls (LAFWs and BSCs), (2) to determine if the opening of syringe and needle packaging overcomes the ability of the primary engineering control to maintain International Organization for Standardization (ISO) class 5 air cleanliness conditions (<3,520 particles per cubic meter [ppcm] or <100 particles per cubic foot [ppcf] of 0.5 μm and larger), and (3) to determine the ability of the LAFW's buffer area to maintain ISO class 7 (<352,000 ppcm or <10,000 ppcf) conditions in dynamic operating situations. We collected data on airborne particulate matter generated during the handling and opening of various syringe and needle packages in LAFWs and BSCs.

To date, only one other published article has examined the generation of particles from supplies and components used in sterile product preparation, and it did not directly address particle counts.[4]

Background

Pharmacists and technicians use approximately 1 billion syringes and needles annually in aseptic compounding. These supplies must be brought into an ISO class 5 primary engineering control while still inside their primary packaging and removed from this packaging just before use. Such engineering controls include LAFWs, BSCs, compounding aseptic isolators (CAIs), and compounding aseptic containment isolators (CACIs). LAFWs and BSCs are to be located in controlled environments that include an ISO class 7 buffer area served by an ISO class 8 (or cleaner) "ante area." Certain isolator designs (including most CAIs and CACIs) that isolate the direct compounding area (DCA) from the buffer area during material transfer and manipulation are currently exempt from these placement requirements.

Buffer areas and ante areas are clean, but they are not sterile or 100% particle-free environments. When properly designed, engineered, built, and maintained, these areas will maintain particle counts that do not exceed 10,000 ppcf (ISO class 7) or 100,000 ppcf (ISO class 8) of air under dynamic conditions. LAFWs, BSCs, and isolators maintain particle counts that do not exceed 100 ppcf (ISO class 5).

Needles and syringes come in a variety of sizes and packaging configurations. Product packages range from blister packages (with a paper or plastic top film and plastic bottom film) to solid plastic cylinders and plastic trays. The manner in which packages are introduced to the compounding area and primary engineering control, wiped down, and removed from packaging will, along with the engineering control design, determine the process-generated contamination in the DCA (the portion within the primary engineering control where "first air"—the unobstructed air exiting the high-efficiency particulate air [HEPA] filter in a unidirectional stream—interacts with the critical site).

Methods

All testing was conducted at a technical training center.[a] The training center has a sterile compounding suite consisting of an ISO class 8 ante area and an ISO class 7 buffer area. A 4-ft LAFW[b] and a 4-ft BSC[c] were located in the buffer area and used for the testing. All engineering controls (producing ISO class 5, 7, and 8 areas) were tested before the study and certified by a qualified technician[d] according to performance standards for each area or device[5-8] and in-process revisions to *USP* chapter 797.[3] The LAFW uses horizontal unidirectional airflow, sweeping air from the HEPA filter across the work surface to the buffer area. The BSC uses vertical unidirectional airflow, sweeping air from the HEPA filter over the work area to the front and rear return grilles.

The LAFW and BSC were cleaned with 70% isopropyl alcohol before testing. During the testing, all personnel present in the buffer area were gowned in accordance with *USP* chapter 797 requirements: hairnet, beard cover if applicable, facemask, gown, and shoe covers. The technician opening the packages wore powder-free nonsterile gloves that were periodically disinfected with a 70% isopropyl alcohol spray throughout the testing. All syringes and needles were removed from their outer cardboard shipping box and placed into plastic containers before entering the buffer area.

All packaging debris generated during the testing was discarded in a trash can in the buffer area. All opened syringes and needles were classified as "clean" sharps and were placed into sharps containers that were disposed of by an approved waste disposal company according to state medical waste regulations.

Packaging configuration. Several different syringe and needle packaging configurations from three vendors were identified and used in the study (Table 1). Some products, including many needles and some of the syringes, came in single packages attached to each other as perforated strip packages. Twelve different products were tested in this study.

Method of opening. Each product packaging configuration was opened by at least two different methods (when feasible) in both LAFW and BSC environments. For the needles and syringes that came in single packages attached to each other with a perforated top web, the generation of airborne particulates was evaluated during separation of the packaging as well as during the opening of individual packages.

Four methods of opening or separating a product's packaging were considered:

Table 1.
Packaged Needles and Syringes Tested

Manufacturer and Catalog Number[a]	Package Type[b]
Needle, 18 gauge	
BD 305196	Soft pack, strip
Tyco 1188818112	Soft pack, strip, all film
Tyco 8881250016	Hard pack, singles
Terumo 3NN-1838R	Soft pack, strip
Syringe, 1 mL	
BD 309628	Soft pack, strip
Tyco 1180100777	Soft pack, strip
Syringe, 10 mL	
BD 309604	Soft pack, singles
Terumo 3SS-10L	Soft pack, singles, all film
Syringe, 12 mL	
Tyco 1181200777	Soft pack, strip
Tyco 8881512878	Hard pack, singles
Syringe, 60 mL	
BD 309653	Soft pack, singles, all film
Tyco 1186000077	Soft pack, strip, all film

[a]Manufacturers were BD, Franklin Lakes, NJ; Tyco (also known as Kendall or Sherwood), Mansfield, MA; and Terumo, Somerset, NJ.
[b]Soft pack = needle or syringe encased between paper and a soft plastic film or between two pieces of plastic film; strip = soft packs of five individually encased needles or syringes joined side by side and separated from each other by tearing a perforation; singles = needle or syringe packages available separately (not joined in a strip); all film = soft pack in which the needle or syringe is packaged between two pieces of plastic film; hard pack = needle or syringe packaged in rigid plastic cylinder.

1. Peel-and-present: This is the manufacturers' recommended method of opening packages. The operator opens the device packaging by peeling the top web from the bottom web, attempting to not tear any part of the packaging.
2. Pop-through: This method is not a recommended technique and is not supported by manufacturers; nevertheless, it is frequently used. The operator opens the device packaging by pushing the device out of the packaging through the paper side of the web, causing a tear in the paper.
3. Twist-off: This is the manufacturers' recommended method of opening certain rigid packages. The operator opens the device by twisting the base cap off the rigid plastic cylinder that contains the device.
4. Burst: The operator takes up strips of product packaging (five units per strip) and quickly separates them into individually packaged devices, which are then opened with either the peel-and-present or pop-through method.

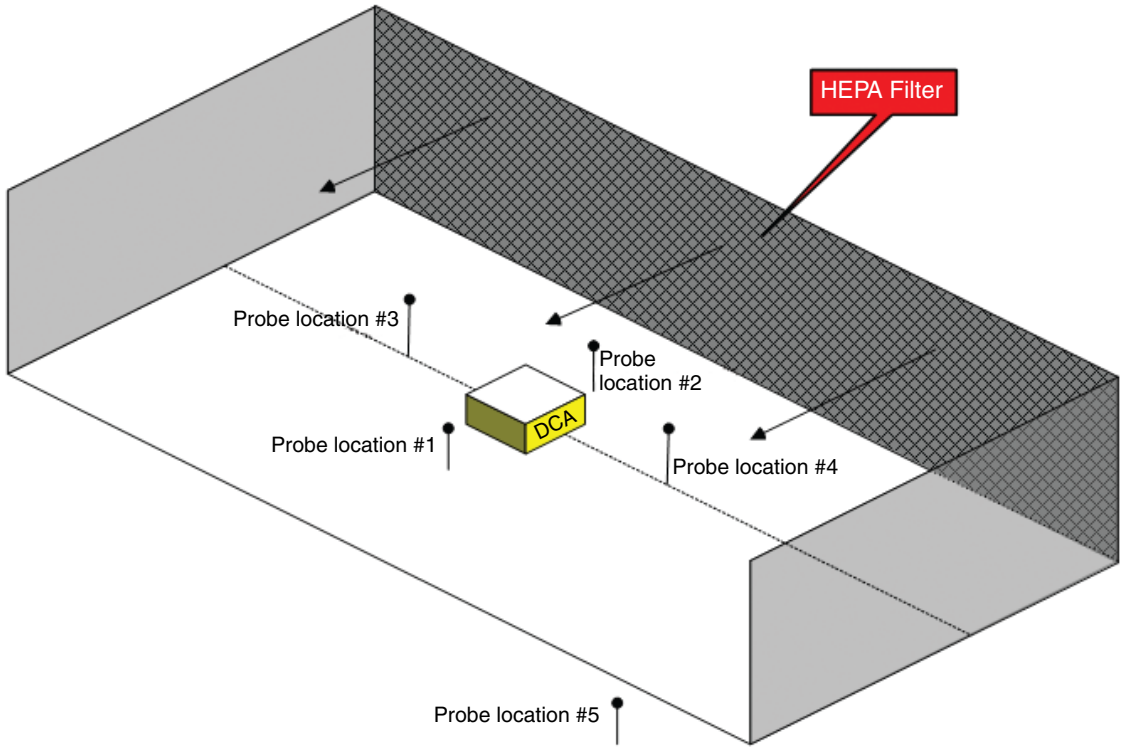
For each method of opening, 25 individual packages of each product configuration were opened. The burst method was used to separate 10 strips of each product that came in this configuration. More than 1500 individual packages were opened during the two-day study.

Particle-count probes. A trained technician performed all package manipulations at a fixed location (the DCA) within the ISO class 5 primary engineering controls (the LAFW and BSC). Four or five particle-count probes were placed at locations within and around the LAFW and within the BSC environments (Figures 1 and 2). For a given engineering control, the DCA remained in a fixed, constant location for all samples tested.

Instrumentation. Each probe was attached to an individual particle counter.[f] Each particle counter was connected to a laptop computer via category-5 Ethernet cable through an Intel five-port network adapter. The data were collected on particle-measurement-system software.[g] Each particle counter was tested, calibrated, and certified before the test; each one sampled at 1 ft^3/min with a minimum sensitivity of 0.3-µm particles. All particle counts reported are for particles of 0.5 µm or larger, and the testing was performed under dynamic operating conditions, unless otherwise stated. The 0.5-µm particle size threshold was chosen on the basis of *USP* chapter 797 and current good manufacturing practices as defined by the Food and Drug Administration. The size range used is generally considered the minimum size of viable particles—those that contain living microorganisms—that travel individually or are the carriers for smaller viable particles. Before the testing, all surfaces (floors, walls, and ceiling) of the ante area and buffer area were mop cleaned and disinfected with a germicidal detergent followed by a 1% sodium hypochlorite rinse.

Statistical methods. *Outcome variable.* The outcome variable was the total number of particles released from a given product packaging configuration opened with a given method. This was calculated by adding the counts for the sampling period from probe #1 (immediately downstream of the DCA) when the LAFW environment was used and the counts from probe #3 (immediately downstream of the DCA) when the BSC environment was used. For example, in the BSC it took 2:11 minutes to open 25 packages of the 18-gauge BD needle by the pop-through method. Probe #3 counted 987 particles, 2026 particles, and 1 particle at times 1:00, 2:00, and 2:11 minutes, respectively. Therefore, the total number of particles for this product and this method of opening in the BSC envi-

Figure 1. Placement of particle-counting probes within the laminar airflow workbench. Probe #1 was placed approximately 7 inches directly downstream of the direct compounding area (DCA), with downstream flow determined by a visual smoke test employing ventilation smoke tubes.[e] This position served as a positive control point, where particles were detected during the smoke test. Probe #2 was placed approximately 7 inches from the face of the high-efficiency particulate air (HEPA) filter in the direct line of airflow, as predetermined by a smoke test, between the filter and the DCA. This position served as a negative control point with a particle count of 5 particles per cubic foot or less during the smoke test. Probes #3 and #4 were placed approximately 12 inches to the left and right, respectively, of the DCA and were as close as possible to the left and right of the operator's hands without particles being detected during a smoke test. Probe #5 was in the buffer area within 4 feet behind and above the operator, where the particle detector captured the accumulation of particles within the area during the smoke test. Arrows indicate direction of airflow.



ronment was 3014 (the sum of the three counts).

Sample size. The sample chosen contained 12 different product packing configurations and 25 individual packages of each configuration as a matter of convenience. No power calculations were done to determine sample size, since the analysis was exploratory in nature.

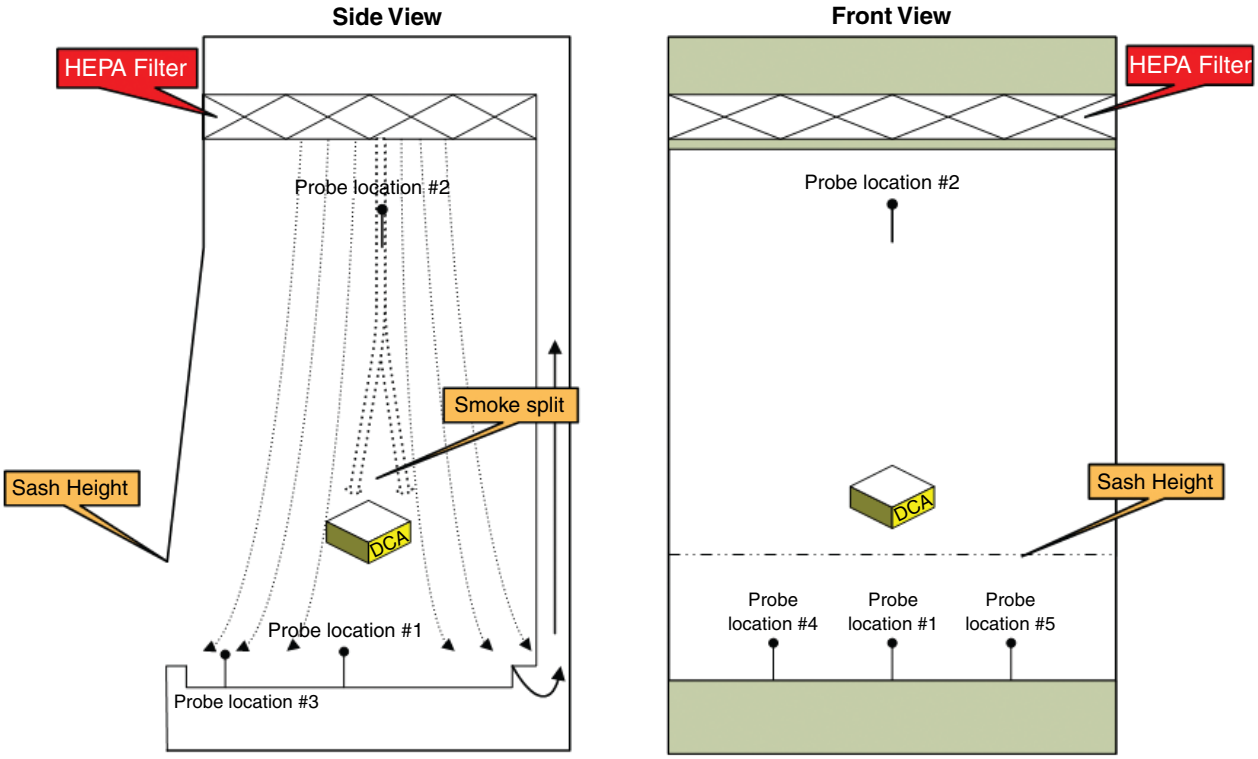
Distributional assumption of outcome variable. The assumption that the total number of particles (0.5 µm and larger) released from a given product was a Poisson-distributed random variable was checked by using a likelihood ratio test based on Poisson and negative binomial distributions (test for overdispersion). There was evidence of overdispersion (the true variance is bigger than the mean).[9,10] Negative binomial regression was used to test the study's hypothesis.

Hypothesis. The purpose of the study was to determine whether there was a difference between the operational LAFW and BSC in total number of particles released into the environment from a given product. In mathematical terms, the logarithm of the mean particle count was modeled as a linear function of the environmental setting. The null hypothesis was that the environmental impact of the operational LAFW is equal to that of the operational BSC, and the alternative hypothesis was that the environmental impact of the operational LAFW was not equal to that of the operational BSC. Negative binomial regression was used to test the null hypothesis.

Results and discussion

The particles detected during the four different syringe-opening exercises fell in two distinct categories: small, nonvisible airborne particles detected only with the particle counters and larger particles visually detected on the work surface. The larger particles were not analyzed as part of this study.

Figure 2. Placement of particle-counting probes within the biological safety cabinet (BSC) as viewed from the side (left panel) and front (right panel) of the BSC. Probe #1 was placed directly under the direct compounding area (DCA) and as close to the work surface of the BSC as the height of the probe and sample tubing would allow. Probe #2 was placed 6 inches below the high-efficiency particulate air (HEPA) filter diffuser and directly above the DCA. This position served as a negative control point with a particle count of 5 particles per cubic foot or less during the smoke test. Probe #3 was placed in the direct route of airflow, as determined by the smoke test, between the DCA and the BSC's intake grille, approximately 1 inch from the grille. Probes #4 and #5 were placed as close as possible to the left and right, respectively, of the operator's hands without particles being detected during a smoke test and as close to the work surface of the BSC as the height of the probe and sample tubing would allow. Arrows indicate direction of airflow.



There was no statistically significant difference between the LAFW and BSC in the numbers of particles generated during package opening. Therefore, reporting here focuses on the following: (1) characterizing the particles generated in the LAFW, (2) describing the numbers of downstream particles detected in the LAFW by probe #1 and in its buffer area by probe #5, and (3) stating whether or not the opening of syringe and needle packaging overcame the ability of the LAFW and the BSC to maintain ISO class 5 or the buffer area to maintain ISO class 7 air cleanliness under dynamic operating conditions. Mean particle counts appear in Table 2.

Some of the products tested had a top and bottom web plastic film package (e.g., BD 60-mL syringe and Terumo 10-mL syringe). Since these packages had no paper component, there did not lend themselves to the pop-through method. When the syringe or needle is pushed through, these packages tend to either not tear at all or tear with extreme difficulty. These all-film packages were opened only with the peel-and-present method. Their opening generated very low concentrations of particles downstream of the DCA. The BD 60-mL syringe averaged 174 ppcf and the Terumo 10-mL syringe averaged 260 ppcf, whereas the paper-based packages averaged 1934 ppcf when opened by the same method.

The hard-pack sterile barrier packages of the Tyco 18-gauge needle and Tyco 12-mL syringe can be opened in only one way (twist-off), and that method generated a very low concentration of airborne particles for both products. The Tyco 18-gauge needle hard pack averaged 42 ppcf, and the Tyco 12-mL syringe hard pack averaged 181 ppcf downstream of the DCA. These packages, however, did generate a small volume of visible plastic "nibs" that were detected on the work surface after the cap was twisted off.

Table 2.
Mean Particle Counts for Products Opened by All Methods (Particles/m³)[a]

Method and Product	Probe Location				
	Downstream[b]	Upstream[c]	Left[d]	Right[e]	Buffer[f]
Peel-and-present[g]					
Needle, 18 gauge					
BD 305196	471	0	1	0	191
Terumo 3NN-1838R	938	0	0	3	833
Tyco 1188818112	520	0	0	0	359
Syringe, 1 mL					
BD 309628	269	0	0	3	649
Tyco 1180100777	6,230	0	0	0	609
Syringe, 10 or 12 mL					
BD 309604	582	0	0	0	488
Terumo 3SS-10L	260	0	0	1	218
Tyco 1181200777	5,713	2	1	7	255
Syringe, 60 mL					
BD 309653	174	0	0	10	223
Tyco 1186000077	4,182	0	17	14	282
Pop-through[h]					
Needle, 18 gauge					
BD 305196	2,472	0	0	0	281
Terumo 3NN-1838R	17,937	0	0	0	545
Syringe, 1 mL					
BD 309628	2,397	0	0	0	403
Tyco 1180100777	34,243	0	0	0	549
Syringe, 10 or 12 mL					
BD 309604	4,512	0	0	0	420
Tyco 1181200777	17,222	0	0	4	418
Twist-off[i]					
Needle, 18 gauge					
Tyco 8881250016	42	0	0	0	466
Syringe, 12 mL					
Tyco 8881512878	181	0	0	0	749
Burst[j]					
Needle, 18 gauge					
BD 305196	1,304	0	0	0	214
Terumo 3NN-1838R	3,761	0	0	8	666
Tyco 1188818112	1,803	0	0	0	447
Syringe, 1 mL					
BD 309628	1,494	1	4	60	447
Tyco 1180100777	1,925	4	0	0	525
Syringe, 12 mL					
Tyco 1181200777	4,659	28	4	128	293
Syringe, 60 mL					
Tyco 1186000077	4,196	37	91	53	567

[a]Unless otherwise noted, results are combined for the laminar airflow workbench (LAFW) and biological safety cabinet (BSC).
[b]Probe #1 in the LAFW and #3 in the BSC.
[c]Probe #2 in the LAFW and BSC.
[d]Probe #3 in the LAFW and #4 in the BSC.
[e]Probe #4 in the LAFW and #5 in the BSC.
[f]Probe #5 outside the LAFW. There was no corresponding probe outside the BSC.
[g]Used for needles and syringes in soft packs.
[h]Used for needles and syringes in soft packs that were not all film.
[i]Used for needles and syringes in hard packs.
[j]Used for needles and syringes in soft pack strips.

Upstream versus downstream particle counts. Sterile compounding should be performed in a unidirectional device, using the first-air concept to facilitate aseptic technique. First air is virtually free of particulate contaminants. All aseptic manipulations must be carried out in the unobstructed first-air zone. As such, the counts upstream of the DCA (first-air) should not exceed 100 ppcf at any time and should not be affected by any process, including package opening within the DCA.

For all samples opened with the peel-and-present, pop-through, and twist-off methods, the number of counted particles measured upstream in the LAFW and BSC averaged 0 ppcf; for the burst method, the upstream count averaged only 10 ppcf. Average downstream counts for all methods exceeded ISO class 5 conditions and were as high as 13,131 ppcf for the pop-through method.

Package separation by burst method. During and after the bursting of 50 packages for all of the paper-backed syringe or needle strip packs, large white paper particles were visually observed and were recorded with a digital camera. A dark plastic sheet was placed on the work surface of the engineering control to facilitate visual inspection. The number and size of these particles were not quantified, but their presence is undesirable and should be avoided.

In addition to these large particles that were observed visually on the work surface, the airborne particulate levels recorded at the left and right probes during the burst method were higher than those during the peel-and-present and pop-through methods. The burst method particle counts for the left and right probes averaged 14 and 36 ppcf, respectively, while peel-and-present averaged only 2 and 4 ppcf, respectively.

In addition, particle counts during the burst method exceeded ISO class 5 (100 ppcf) air cleanliness for one of the packages (Tyco 10- or 12-mL syringe) with a right probe count of 128 ppcf. After strip-packaged products were separated, opening with the peel-and-present and pop-through methods resulted in particle counts of 0 ppcf at the upstream, left, and right probes, except for the Tyco 60-mL and 10- or 12-mL syringe packages.

Given the data and the large visible particles, strip packages should be separated and wiped down outside the buffer area to prevent the release of large particles within the primary engineering control, buffer area, and storage bins.

Pop-through versus peel-and-present Method. For the peel-and-present method, which is recommended by manufacturers, the average downstream particle counts were much lower than for the pop-through method. For example, the particle count for the 18-gauge Terumo needle was only 938 ppcf for peel-and-present but was 17,937 ppcf for pop-through.

The pop-through method of handling the device packaging generates a very high level of particulates within the ISO class 5 engineering control and should be avoided. Instead, the peel-and-present method should be used.

Impact on the ISO class 7 buffer area. The impact on the buffer area particle counts of opening packages in the LAFW was determined by comparing the background counts with the levels measured by probe #5 during testing. Background counts in the buffer area in the vicinity of the testing ranged from 411 to 608 ppcf before testing began. The average particle count in the buffer area during the package opening procedures was 482 ppcf. The highest count at any time in the buffer area during the package opening procedures was 1906 ppcf. At no time did the counts in the buffer area exceed ISO class 7 conditions.

The buffer area air exchange rate, including the HEPA-filtered air from the primary engineering control, was 81 air changes per hour (ACPH), which exceeds the minimum ACPH specified in *USP* chapter 797. Chapter 797 requires at least 30 ACPH (with no less than 15 ACPH from the room if using HEPA-filtered air from the primary engineering controls in the air change calculation) for the ISO class 7 buffer area.

Implications. Primary engineering controls used in sterile compounding typically employ unidirectional airflow designed to sweep the DCA with particulate-free, HEPA-filtered air (first air); this eliminates outside contamination and removes process-generated contamination. A comparison of the particle counts recorded at the various probe locations demonstrated the effectiveness of the unidirectional airflow in particulate removal. Regardless of particle counts downstream of the DCA, the particle counts upstream of the DCA were within ISO class 5 air cleanliness standards. Performing all package manipulation downstream of the DCA and keeping a clear zone 12 inches on both sides will ensure that this required level of air cleanliness is maintained. Packages should never be manipulated directly in front of or over opened vials, ampuls, or other sterile compounding supplies.

Before any supplies are placed in the primary engineering control, all items must be wiped down with a 70% isopropyl alcohol-wetted wipe and the supplies' outer packaging must be removed. The separation of packages (burst method) creates a significant burden of large particulates that is not easily controlled by the unidirectional airflow. An efficient way to control the particulate burden from this process is to separate packages outside the aseptic compounding environment before wiping down the separated packages and transferring them into the buffer area.

Both horizontal and vertical unidirectional airflow in the devices

used for this study effectively controlled the particulate burden created by opening the packages. Well-ventilated buffer areas with HEPA-filtered air do not appear to be affected by particulate release during the opening of syringe and needle packages in the LAFW.

Conclusion

All methods of separating and opening the packaging of needles and syringes generated particles. The peel-and-present technique generated the lowest particulate volume. The LAFW and BSC were equally effective in maintaining low particle counts.

[a]Micro-Clean, Inc. Bethlehem, PA.

[b]Horizontal LAFW (model NU-201-430), serial no. 14854SV, NuAire, Plymouth, MN.

[c]Forma class II, type A1 BSC (model 1200), serial no. MCI04605, Thermo Scientific, Waltham, MA.

[d]An employee of Micro-Clean, Inc.

[e]Ventilation smoke tubes, Drager Safety AG & Co., Germany. The filling layer of the airflow tube is impregnated with fuming sulfuric acid. When air is pumped into the tube by means of the rubber bulb, sulfuric acid aerosol emerges in the form of white smoke.

[f]Lasair-II 310-A particle counters (serial nos. 49348, 49373, 49375, 49376, and 39242), Particle Measuring Systems, Boulder, CO. Each particle counter was certified by the manufacturer to meet or exceed all published specifications and was calibrated within the previous six months using equipment and standards of accuracy specified by the National Institute of Standards and Technology.

[g]Pharm Net version 3.0, Particle Measuring Systems, Inc., Boulder, CO.

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