SURROGATE POWDER AND ASHRAE-110 TESTING OF A MULTI-PURPOSE ENCLOSURE FOR WEIGHING/SIEVING/FLUID BED DRYER APPLICATIONS

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Introduction

Advances in the pharmaceutical industry have led to increased potency and increased receptor selectivity of Active Pharmaceutical Ingredients (APIs). While this leads to more effective drug treatments for patients, the increased potency puts the pharmaceutical laboratory worker at a greater risk of exposure to harmful compounds at lower exposure levels. This drives the need for increased safety measures for better worker protection in the laboratory.[1]

There are numerous categorization systems to quantify the hazards that certain APIs pose to the worker. One system used to rate the potency of a substance is outlined by the International Society of Pharmaceutical Engineering (ISPE), in which compounds are placed into four categories with defined Occupational Exposure Limits (OELs).[2] Compounds placed in Category I are generally low in potency and have an OEL of 100 µg/m^3 or greater. Category II includes APIs that have a higher toxicity and have an OEL range between 20 µg/m^3 and 100 µg/m^3. Category III compounds are considered potent and/or toxic, and their OEL range is between 5 µg/m^3 and 20 µg/m^3, and highly potent compounds in Category IV have an OEL of below 5 µg/m^3.

To properly protect the laboratory workforce, engineering controls must be put in place to provide appropriate containment of APIs. These controls should be designed to contain the API source as close to the source and as far away from the worker as possible.[1] For Categories II, III, and IV of the ISPE hazard categorization system, containment equipment is recommended to reduce potential exposures of APIs. Containment equipment include completely enclosed units such as isolators and soft-walled units as well as ventilated enclosures with open ventilated work zones. With good standard operating procedures (SOPs) and skilled, trained workers, low-flow ventilated enclosures are an effective engineering control to provide containment of equipment and processes involving potent APIs.

This article describes the performance testing of the Flow Sciences Multi-Purpose Enclosure, which was designed to contain potent APIs for an 8-hour Time Weighted Average (TWA) OEL of less than 10 µg/m^3. The Factory Acceptance Testing (FAT) consisted of an ANSI/ASHRAE-110 test[3] as well as a containment verification assessment following the ISPE Guide "Assessing the Particulate Containment Performance of Pharmaceutical Equipment," also known as the SMEPAC guide.[4] The containment verification assessment was performed following a sampling strategy that was designed to evaluate the containment capabilities of the enclosure for three different operations: a bulk powder weighing operation, a sieving operation, and a fluid bed dryer operation. Testing was performed utilizing three different operators to evaluate the potential for operator variability in using the enclosure. The testing was overseen by a third party consultant, IES Engineer's Certified Industrial Hygienist (CIH) in accordance with: best Industrial Hygiene practices; the guidelines published in Section II, Sampling, Measurement, Methods, and Instruments, of the Federal Occupational Safety and Health Administration (OSHA) Technical Manual; and the ANSI/ASHRAE and ISPE Guide listed above.

Testing results for all three applications using three different operators at varying skill levels showed that the enclosure successfully contained the surrogate powder for each operation at a level less than 1 µg/m^3, significantly below the customer's required OEL. The testing demonstrated the ability of the Multi-Purpose Enclosure to contain APIs in the ISPE categorization system down to the Category IV hazard levels.

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Description of Enclosure

The custom-designed enclosure is a 79” wide, 40” deep, 38” high unit made of polypropylene construction with a phenolic base, and is shown in Figure 1. The right side of the enclosure base has a large cutout that accepts a roll-in cart of similar size so that different pieces of equipment can be rolled into the enclosure for different operations. This allows the user to operate multiple pieces of equipment with one enclosure, which increases the overall floor space in the lab, reduces the amount of flow requirements for the room, and reduces capital equipment budget outlay. The entire enclosure is supported by an ADA-compliant electronically controlled lift table so that the operator can vary the enclosure height for the optimal ergonomic position.

Three different roll-in carts were designed for use with the enclosure. The top base of each cart is designed to be used with different pieces of equipment or processes. One cart top is designed for a bulk powder transfer operation, wherein a drum of material is placed on a drum lift cart and slid underneath the bulk powder cutout of the cart (see Figure 1). The drum lift raises the drum through the cutout, and a series of membranes provides a seal between the drum and the enclosure, preventing any API from escaping through the cutout. A second cart was designed to have a stainless steel dished base to support a Strea-1 fluidized bed dryer. The enclosure was designed with an interior “trunk” that attaches to the exit of the fluid bed dryer and carries the dryer’s exhaust out through the house exhaust system. A third cart was designed to accommodate an L1A Fitzmill. In the current study, surrogate powder testing was performed using the bulk powder cart for the weighing and sieving operations and one of the dished based carts for the fluidized bed dryer application.

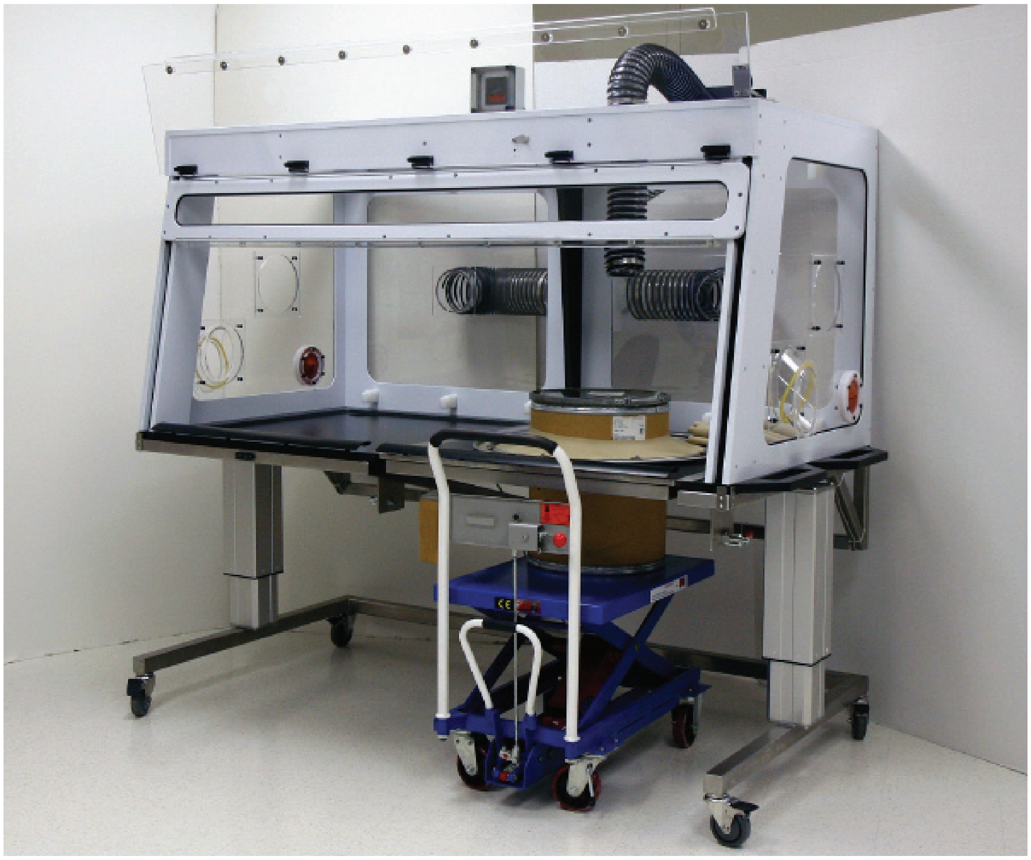

Figure 1. Flow Sciences Multi-Purpose Enclosure.

Experimental Setup

The ASHRAE-110 test method consists of three components: 1) an average face velocity measurement, 2) a smoke visualization test, and 3) a tracer gas test. All testing was conducted according to guidelines outlined in the ANSI/ASHRAE 110-1995 document "Method of Testing Performance of Laboratory Fume Hoods"[3] as well as the ISPE Published Guide "Assessing the Particulate Containment Performance of Pharmaceutical Equipment – A Guide."[4] All sampling was performed under the direction of the IES CIH who verified experimental set-up and sampling strategy for the operations tested.

A Dwyer 471 digital anemometer was used to take velocity measurements across the face of the enclosure. A small smoke tube containing titanium tetrachloride was used for local smoke generation, while a theatrical smoke generator was used to generate a large volume of smoke and determine the clearance time of the enclosure. The tracer gas used in the experiments was 99.95% pure sulfur hexafluoride, set at a flow rate of 4.0 Lpm. The tracer gas ejector system is equivalent to the ANSI/ASHRAE-110 standard ejector system, and the tracer gas detection instrument was a Miran 205E SapphIRe portable ambient air analyzer. A three-dimensional manikin of reasonably human proportions was used in the tracer gas testing.

The lactose used as the surrogate powder was Impalpable 313 monohydrate, which is a spray-dried white crystalline powder, prepared with a 325 mesh screen, resulting in 60% of the particles being less than 45 microns in size. The lactose did not contain any whey or whey products. Air samples were collected using Sensidyne Gil-Air 5 pumps, which were calibrated using the primary standard bubble meter method. The sampling pumps were adjusted to 2.0±0.1 Lpm prior to each sampling period. The flow rate for all air sampling pumps was assumed to remain constant throughout the entire sample period. There is an automatic flow fault indicator which will light up if the pump is unable to maintain flow rate within ± 5 % of the set point. There were no sampling pump failures during any of the trials. The sampling filters were two piece 25 mm preloaded cassettes from SKC, and PTFE filters were used as the sampling media.

The operator breathing zone was defined as a 6-9" hemisphere forward of the shoulders, roughly from below the eyes to the lapels. Each operator wore two sampling pumps that were kept attached to the left and right pockets, with the filters attached to either side of the operator's collar. After each operator completed his operation both breathing zone filters were changed. Four area sampling pumps were positioned around the operator during each trial (see Figure 2 for sample pump placement). Sampling pumps were placed 6" in front of either side of the enclosure on small metal portable stands. A third pump was placed under the enclosure near the seal between the front corner of the cart and the enclosure, 6" from the underside of the base. A fourth pump was centered 5' back from the front of the enclosure behind the operator, and one sampling pump was placed inside the enclosure towards the back plenum. After each operator had performed the same operation (either the weighing, sieving, or fluid bed drying), the four area filters were changed. Another sampling pump was placed in the center of the lab the day before the test and used to capture a background sample. Three separate background samples were run overnight prior to the testing the following day. An average concentration of 0.015 µg/m³ was detected.

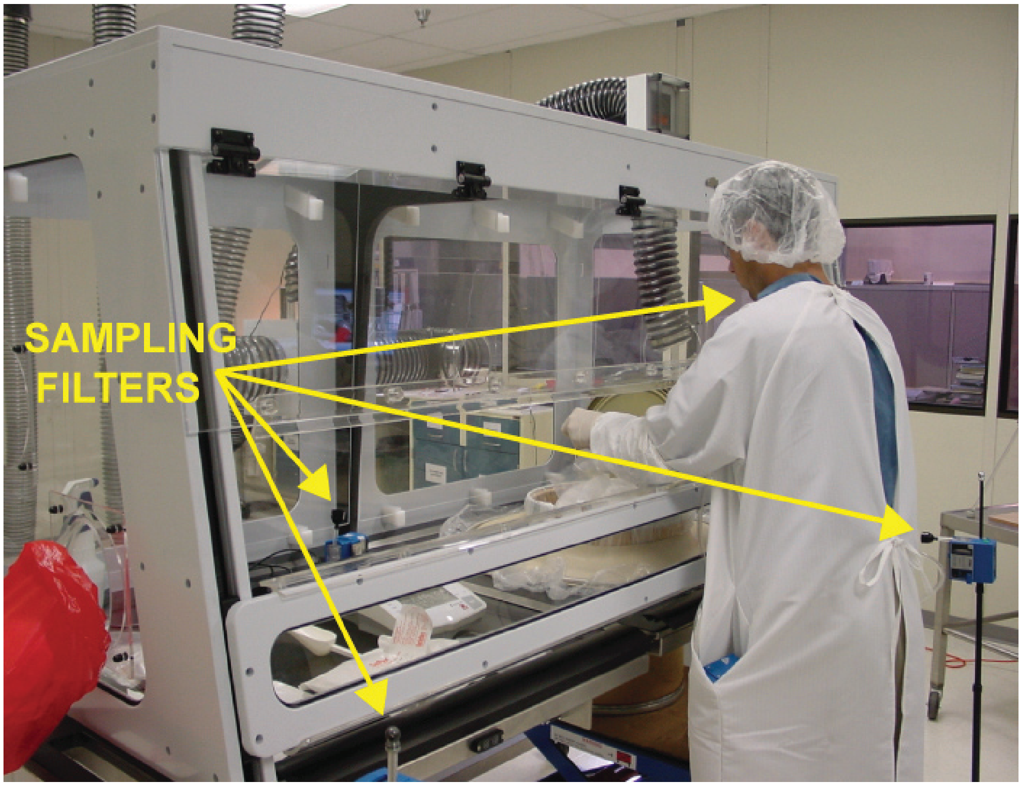

Figure 2. Sampling pump placement in laboratory.

Description of Operations

Three different operations were performed in the enclosure: 1) a bulk powder weighing operation, 2) a sieving operation, and 3) a fluid bed drying operation. Each procedure is described in detail in the following sections:

Bulk Powder Weighing

The operator begins this operation by placing a 25-kilogram drum of lactose onto the rolling drum cart lift. The cart is then rolled into position underneath the removable bulk powder cutout. The operator raises the lactose drum so that the top of the drum protrudes through the rubber membranes. The lactose drum lid is removed and placed inside the right side of the enclosure. Each bag of the double-bag configuration is opened, and a series of membranes and retaining rings hold the bags open and ensure no contaminant escapes through the cutout. The operator uses a scoop to transfer lactose powder from the drum into a plastic bag, which is then weighed on a balance located on the left side of the enclosure. Four bags, each containing 250 g of lactose powder, are weighed out, for a total of 1 kg per operator. Once the bags are weighed out and left on the left side of the enclosure, the operator closes up the lactose drum, wipes down all surfaces, and places his disposable personal protective equipment and wipes into the waste chute.

Sieving

The operator scoops out 250 g of lactose powder from a pre-weighed plastic bag and places the lactose into the top of a sieve. The operator then shakes the sieve so that fine powder is collected in the bottom pan. This collected powder is transferred to another plastic bag. This process is repeated three more times so that a total of 1.0 kg of lactose is sieved, the contents of which are then weighed using a balance.

Fluid Bed Dryer

The fluid bed dryer was placed on the removable cart base and rolled into the cutout of the enclosure. A pre-weighed sample of 500 g of lactose was placed in the fluid bed dryer container. The fluid bed dryer was turned on and the flow rate of heated air was adjusted so that the powder in the container was allowed to rise halfway up the container. The operator continuously adjusted the flow rate (between 30 – 60% of the maximum flow rate) to obtain this powder level. The fluid bed dryer was operated for ten minutes and then the dried powder was scooped out from the container and transferred to a plastic bag. Another sample of 500 g of lactose was placed in the fluid bed dryer container and the same procedure was followed. The entire 1.0 kg was then weighed on a mass balance. The operator then wiped down all work surface areas as well as the fluid bed dryer.

All three operators are full-time employees of Flow Sciences, and all of them completed each of the preceding operations once during the testing. A summary of operator background and amount handled with each process is provided in Table 1.

Operator	**1**	**2**	**3**
Gender	Male	Male	Male
Profession	Engineer	Lab Technician	Quality Control Lead
Skill Level	Moderately Skilled	Unskilled	Unskilled
Weighing Amount	1.0 kg	1.0 kg	1.0 kg
Sieving Amount	1.0 kg	1.0 kg	1.0 kg
Fluid Bed Dryer Amount	1.0 kg	1.0 kg	1.0 kg

Table 1. Operator background and weighing amount.

ASHRAE-110 Testing Results

Results of the ASHRAE-110 testing are given below and summarized in Table 2.

Face Velocity Measurements

Enclosure face velocities were taken every 6” across the plane of the face opening. At each location 25 face velocity readings were taken and averaged to obtain an average reading at each location across the center of the face opening. With the laboratory exhaust ventilation set at 375 CFM, the average face velocity of the enclosure was measured to be 73 fpm. The maximum average reading at any location was measured to be 79 fpm, while the minimum average reading at any location was measured to be 69 fpm. This shows a consistent velocity profile across the face opening of the enclosure, resulting in a smooth, laminar flow across the work surface.

Flow Visualization

The local flow visualization tests using a smoke stick showed smooth laminar flow across the face opening of the enclosure. The flow swept laterally across the work surface, and no reversions of flow were seen across the face opening. The large volume smoke test using the theatrical smoke generator also showed no reversions across the face opening. The clearance time for the high volume smoke test was measured to be 69 seconds.

Tracer Gas Test

The average concentrations of sulfur hexafluoride measured during the tracer gas test were below the instrument's level of detection of 10 ppb, with one maximum transient reading of 15 ppb. These results indicate an acceptable level of containment, well below the SEFA industrial standard of 50 ppb. Based on the measured concentrations the enclosure receives an As Manufactured (AM) rating of AM 0.005.

Average Face Velocity	73 fpm
House Exhaust	375 CFM
Smoke Clearance Time	69 sec
Average Tracer Gas Reading	< 10 ppb
Maximum Tracer Gas Reading	15 ppb

Table 2. Summary of ANSI/ASHRAE-110 testing.

Surrogate Powder Testing Results

The test results for the bulk powder weighing operation for all three operators are shown in Table 3. The four Area samples (excluding the background sample) were running continuously during each operator's procedure, and so are indications of the surrogate concentration for all three operators combined. The Background Area sample was collected the night before the assessment took place. All Area samples with the exception of "Right Edge 6" in Front" were below 0.050 µg/m^3. This errant Area sample, which had a concentration of 0.414 µg/m^3, indicates that there may have been some leakage of lactose on the right side of the enclosure, where the bulk powder drum is located.

The highest surrogate concentration at the breathing zone for Operator 1 was 0.091 µg/m^3, which is well below the required OEL level of 10 µg/m^3. Operator 2, one of the inexperienced operators, was exposed to higher concentrations of lactose with a peak of 2.25 µg/m^3. The third operator had an exposure in between that of the other operators, with a peak of 0.652 µg/m^3. The average surrogate concentration of the breathing zones of all operators for the entire bulk powder weighing operation was determined to be 0.733 µg/m^3, which is well below the required OEL level of 10 µg/m^3. This operation illustrates the dependence on operator skill and variability when performing the same process in the same type of containment device: an unskilled operator can be exposed to a significantly higher amount of contaminants than an operator with a basic training of the processes and use of the equipment.

Sample Description	Operator	Duration (min.)	Surrogate Concentration (µg/m³)
Overnight Background	Area	716	0.010
Right edge 6 " in front	Area	105	0.414
Left edge 6 " in front	Area	105	0.010
Room background 5' in front	Area	105	0.045
Under enclosure	Area	105	0.042
Left operator BZ	1	28	0.091
Right operator BZ	1	28	0.084
Left operator BZ	2	26	2.250
Right operator BZ	2	26	0.994
Left operator BZ	3	24	0.329
Right operator BZ	3	24	0.652
Blank			<0.029
Average Operator BZ			0.733

Table 3. Test results for bulk powder weighing application.

The test results for the sieving operation are shown in Table 4. All Area samples show similar concentrations and are all below 0.08 µg/m^3, indicating that there were no significant leakage events for any operator during the entire sieving process. The peak concentration measured at Operator 1's breathing zone was 0.282 µg/m^3, the peak for Operator 2 was 0.612 µg/m^3, and the peak for Operator 3 was 0.129 µg/m^3. All of these values are similar in magnitude and are far below the required OEL level of 10 µg/m^3. The average concentration of all operators for the entire sieving process was calculated to be 0.270 µg/m^3.

Sample Description	Operator	Duration (min.)	Surrogate Concentration (µg/m³)
Overnight Background	Area	909	0.012
Left edge 6 " in front	Area	115	0.026
Right edge 6 " in front	Area	115	0.042
Room background 5' in front	Area	115	0.075
Left operator BZ	1	33	0.067
Right operator BZ	1	33	0.282
Left operator BZ	2	34	0.429
Right operator BZ	2	34	0.612
Left operator BZ	3	48	0.129
Right operator BZ	3	48	0.103
Blank			<0.002
Average Operator BZ			0.270

Table 4. Test results for sieving application.

The test results for the fluid bed dryer operation are shown in Table 5. All Area samples show similar concentrations and are all below 0.14 µg/m^3, indicating that there were no significant leakage events for the fluid bed drying tests. The peak concentration measured at Operator 1's breathing zone was 0.131 µg/m^3, the peak for Operator 2 was 0.796 µg/m^3, and the peak for Operator 3 was 0.117 µg/m^3. All of these values are similar in magnitude and are far below the required OEL level of 10 µg/m^3. The average concentration of all operators for the entire sieving process was calculated to be 0.291 µg/m^3.

Sample Description	Operator	Duration (min.)	Surrogate Concentration (µg/m³)
Overnight Background	Area	716	0.010
Right edge 6 " in front	Area	125	0.092
Left edge 6 " in front	Area	125	0.008
Room background 5' in front	Area	125	0.138
Under enclosure	Area	125	0.068
Left operator BZ	1	39	0.131
Right operator BZ	1	39	0.059
Left operator BZ	2	43	0.796
Right operator BZ	2	43	0.529
Left operator BZ	3	45	0.110
Right operator BZ	3	45	0.117
Blank			<0.002
Average Operator BZ			0.291

Table 5. Test results for fluid bed dryer application.

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Conclusion

The Flow Sciences Multi-Purpose Enclosure has been shown to successfully provide containment for a variety of processes including bulk powder weighing, sieving, and a fluid bed dryer operation, validating its use for applications involving OELs less than 10 $\mu g/m^3$. The ANSI/ASHRAE-110 testing method and surrogate powder testing using lactose were used to test the enclosure.

The exposure levels measured for the weighing operation at the operator breathing zone ranged between 0.084 $\mu g/m^3$ for the moderately skilled operator and 2.25 $\mu g/m^3$ for one of the unskilled operators. This variability in level of exposure control illustrates the correlation between operator skill, training and technique and effectiveness of exposure control provided by a low flow enclosure. The sieving and fluid bed drying operations also show this trend, with the moderately skilled operator achieving exposure levels lower than Operator 2, one of the unskilled operators.

It is important to note, however, that all three operators were exposed to OELs of less than 3 $\mu g/m^3$ in every operation, and thus could safely work in the enclosure for all operations. This assessment has therefore validated that the Flow Sciences Multi-Purpose Enclosure is a proper engineering control to provide containment of APIs below 10 $\mu g/m^3$.

References

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[4] International Society for Pharmaceutical Engineering, “ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment,” First Edition, January 2005.

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